# ASYMMETRIC METATHESIS REACTIONS INVOLVING ACHIRAL AND MESO SUBSTRATES

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## Field of Invention

The present invention relates generally to organometallic catalysts for the formation of optically pure compounds. These compounds can be formed by olefin metathesis reactions such as ring-closing metathesis (RCM), ring-opening metathesis and cross-metathesis. The present invention also provides a method for converting achiral or meso substrates into at least one enantiomer of a product.

## Background of the Invention

The formation of carbon-carbon bonds remains among the most important reactions in synthetic organic chemistry. Consequently, the development of transition metal catalyzed carbon-carbon bond formation represents a significant advance in organic synthesis. In addition, the formation of optically pure compounds via enantioselective catalysis is highly desired.

One reaction involving transition metal catalyzed carbon-carbon formation is olefin metathesis. Olefin metathesis can be defined conceptually as a mutual exchange of alkylidene units between two olefins involving both the formation and cleavage of carbon-carbon double bonds. Transition metal ion catalysts allow this reaction to proceed in a facile manner through a [2+2] cycloaddition between an M=C center and a carbon-carbon double bond. When two olefin groups are located on the same molecule and are subjected to olefin metathesis conditions, a ring-closing metathesis (RCM) reaction can occur in which a series of olefin metathesis reactions produce a cyclic olefin. Ring-closing metathesis is most facile for 5 - 7 membered ring systems because of the low ring strain afforded by these compounds. Ruthenium and molybdenum alkylidene complexes have proven capable of ring closing dienes having a variety of functional groups.

RCM reactions are generally plagued by undesirable reactions that compete with ring formation, such as acyclic diene metathesis, dimer formation and ring opening metathesis. The former reaction can involve polymer formation through the metathesis of terminal dienes whereas the latter reaction comprises metathesis reactions of the ring-closed cyclic olefin. These competing reactions can be circumvented, for example, by performing the reactions under dilute conditions, optimizing ring sizes and by varying the type and extent of olefin

substitution. The latter strategy is also useful for directing the initial reaction of the metal alkylidene towards one olefinic site in a diene over the other olefinic group.

The development of asymmetric ring closing metathesis has considerable potential as a powerful synthetic tool for the preparation of ring structures of defined stereosymmetry. For example, a logical application of asymmetric RCM is the synthesis of natural products which contain varying sizes of ring systems having pendant functional groups of specific stereosymmetry. U.S. Patent No. 5,516,953 discloses a process for the preparation of optically active cycloolefins catalyzed by molybdenum and tungsten complexes. This process requires that substrate be initially isolated as an optically active diene or an achiral, symmetrical polyolefin (i.e. a desymmetrization reaction). Olefin metathesis is catalyzed by molybdenum and tungsten halide or oxide complexes that may also contain alkoxide or amido ligands. In some instances, a tin, lead, aluminum, magnesium or zinc complex cocatalyst may be required.

U.S. Patent No. 4,654,462 describes a process for olefin metathesis by a tungsten complex containing two phenoxy groups, a halogen atom, an alkyl radical and a carbene. Stereoselectivity is reported sufficient to control cis/trans isomerization in the metathesis of pure cis or trans olefins.

Only recently, the first report of an asymmetric RCM reaction involving the interaction of a chiral catalyst with a racemic substrate mixture was reported by Grubbs et al. *J. Am. Chem. Soc.* **1996**, *118*, 2499, *Organometallics* **1996**, *15*, 1865. A racemic diene substrate was added to a molybdenum alkylidene amido catalyst containing a dialkoxide ligand. At various conversion levels of the starting mixture, the enantiomeric excess of the unreacted diene mixture was analyzed, resulting in enantiomeric excess values of up to 48 %. The enantiomeric excess of the ring-closed product was not reported. It was proposed that the dialkoxide had a rigid structure suitable to promote the transfer of asymmetry.

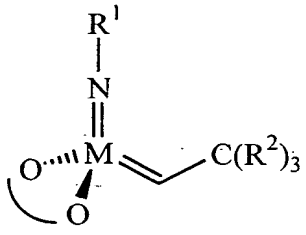
There remains a fundamental need for the synthesis of optically pure products by using asymmetric ring-closing metathesis reactions. In a recent review article, Blechert et al. discuss the state of the art relating to asymmetric RCM reactions, maintaining that "In light of the e.e. [enantiomeric excess] values obtained to date, synthetic applications of this process are currently not envisioned." *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. Asymmetric processes only begin to show promise industrially when achieving enantiomeric excess values of at least 80 %.

Another class of reactions that further advances the field of asymmetric synthesis is enantioselective desymmetrization reactions. The desymmetrization process involves converting achiral or meso substrates, i.e. substrates having a plane of symmetry, into a molecule having a stereocenter. If the desymmetrization reaction can be carried out enantioselectively, then one enantiomer is produced selectively in high enantiomeric excesses. In particular, desymmetrization reactions involving carbon-carbon bond formation have great potential in the pharmaceutical industry and in natural products synthesis, and only a limited number of examples have been reported in the literature. In Trost et al., palladium-catalyzed cyclization reactions yield chiral products having enantiomeric excesses of no more than 90%. Higher enantiomeric excess values can be obtained but only in the presence of added triethylamine. *J. Org. Chem.* **1998**, *63*, 1339-1341. In Mikami et al., carbon-carbon bond formation is effected between two substrates in an enantioselective fashion in the presence of a chiral titanium complex. *J. Am. Chem. Soc.* **1992**, *114*, 6566-6568. The field of asymmetric synthesis, however, remains wide open to increase the variety of desymmetrization reaction types and to improve synthetic conditions such as lower catalyst loadings, increased yields and conversions and decreased reaction times.

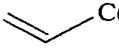
It remains a challenge to design a metal catalyst that can catalytically generate compounds having stereocenters while achieving high enantioselectivity.

## Summary of the Invention

In one illustrative embodiment of the present invention, a composition is provided having the structure:

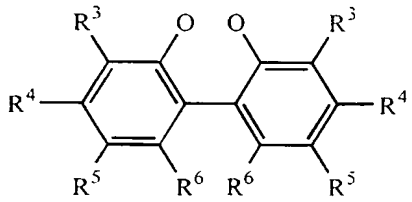


I

The composition has a chiral dialkoxide ligand, denoted by  , wherein the dialkoxide is of at least 80 % optical purity. A  reaction site is of sufficient shape specificity, defined in part by the dialkoxide of sufficient rigidity and a M=N-$R^1$ site to cause a mixture of

two enantiomeric olefins to react with an M=C center of the M=C($R^2$)$_3$ reaction site at different rates. The reaction is an olefin metathesis reaction and the product has at least a 50 % enantiomeric excess of one enantiomer present in the original mixture. M is a metal ion, preferably molybdenum or tungsten.

In one embodiment of the invention, the group of atoms defining the shortest chemical bond pathway linking the oxygen atoms in  contains at least four atoms. In another illustrative embodiment of the present invention,  comprises the structure:



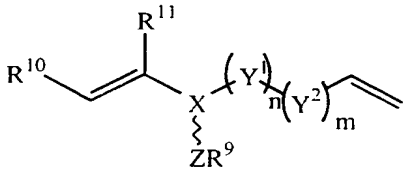
II

The chiral dialkoxide transfers asymmetry to the composition such that the composition is at least 80 % optically pure.

In another embodiment of the present invention, a method is provided wherein a diene mixture of enantiomers is reacted with the M=C center of the above-mentioned composition. The method involves allowing a first enantiomer of the mixture to metathesize at M to an extent greater than a second enantiomer to form a product that has an enantiomeric excess of at least 50 %. The metathesizing step occurs catalytically.

One aspect of the invention provides a method which includes a step of adding the racemic diene mixture to produce a ring-closed metathesis compound having an enantiomeric excess of at least 50 % at 50 % conversion of the diene mixture. Moreover, the enantiomeric excess of an enantiomer in the unreacted diene mixture is at least 50 % at 50 % conversion. The method allows 50 % conversion of the racemic diene mixture to be achieved within a time of at least 1 second.

In another illustrative embodiment of the present invention, the diene comprises the structure:



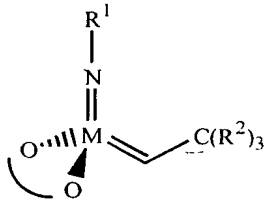
III

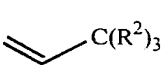
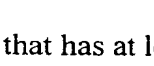
The diene contains one unsubstituted olefin group and one hindered olefin group to direct the initial metathesis towards the unsubstituted end. Reaction of the diene with the composition results in the formation of a ring-closed compound. The diene has a stereocenter and is available as a racemic mixture.

Another aspect of the invention provides a method for desymmetrization. The method involves the step of providing a molecular substrate having a plane of symmetry. A desymmetrization reaction is allowed to occur to form a product free of a plane of symmetry. In another aspect, the desymmetrization is allowed to occur in the absence of solvent.

Another aspect of the invention provides a method for catalytic desymmetrization. The method involves the step of providing a molecular substrate having a plane of symmetry and providing a catalyst. A desymmetrization reaction is allowed to occur to form a product having a tertiary or quaternary carbon center in at least about 20% enantiomeric excess.

Another aspect of the invention provides a composition comprising a structure:



M is a metal ion and  is a chiral dialkoxide of at least 80 % optical purity. The dialkoxide has sufficient rigidity such that a  reaction site is of sufficient shape specificity, defined in part by the dialkoxide and a M=N-R site, to cause a molecular substrate having a plane of symmetry to react with a M=C center at the  reaction site. A catalytic olefin metathesis product is formed that has at least a 50 % enantiomeric excess of at least one enantiomer present in the mixture. The product is free of a plane of symmetry.

Another aspect of the present invention provides a method for performing a kinetic

resolution. The method involves providing at least one substrate having at least one olefin group. The method further comprises selecting a catalyst of sufficient steric bulk to initiate an olefin metathesis reaction involving the at least one substrate to achieve a $k_{rel}$ of at least about 10.

Another aspect of the present invention provides a method for performing an asymmetric olefin metathesis reaction. The method comprises providing a substrate comprising at least one olefin group associated with a ring structure. A catalyst is reacted with the substrate to initiate an olefin metathesis reaction to achieve a $k_{rel}$ of at least about 5.

Another aspect of the present invention provides a method for performing an asymmetric olefin metathesis reaction. The method involves providing two substrates, each substrate containing at least one olefin group. The method also involves reacting a catalyst with the substrates to form a product having an enantiomeric excess of at least about 50%.

Other advantages, novel features, and objects of the invention will become apparent from the following detailed description of the invention when considered in conjunction with the accompanying drawings, which are schematic and which are not intended to be drawn to scale. In the figures, each identical or nearly identical component that is illustrated in various figures is represented by a single numeral. For purposes of clarity, not every component is labeled in every figure, nor is every component of each embodiment of the invention shown where illustration is not necessary to allow those of ordinary skill in the art to understand the invention.

## Brief Description of the Drawings

Fig. 1 depicts a proposed mechanism for a ring-closing metathesis catalytic cycle, illustrating the reaction intermediates; and

Fig. 2 shows example catalysts;

Fig. 3 shows a schematic of the formation of 5-membered rings by ARCN;

Fig. 4 shows a schematic of catalytic enantioselective carbocycle synthesis by ARCN;

Fig. 5 shows structures of substrates for catalytic enantioselective heterocycle synthesis by ARCN;

Fig. 6 shows structures of substrates for enantioselective synthesis of six-membered ring heterocycle by Mo-catalyzed desymmetrization;

Fig. 7 shows a schematic reaction of enantioselective ring-opening/cross-metathesis

reaction;

Fig. 8 shows another schematic of enantioselective ring-opening/cross-metathesis reaction;

Fig. 9 shows a schematic of ring-opening/cross-metathesis for a variety of styrene substrates;

Fig. 10 shows a series of kinetic resolutions of acyclic dienes;

Fig. 11 shows a schematic of a determination of stereochemistry;

Fig. 12 shows a schematic for the formation of binaphthol ligands;

Fig. 13 shows a schematic of a determination of stereochemical identity of catalytic desymmetrization products;

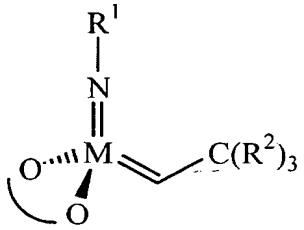
Fig. 14 shows structures of substrates for desymmetrization for tetraenes by Mo-catalyzed ARCN;

Fig. 15 shows structures of substrates for desymmetrization of trienes by tandem Mo-catalyzed ring-opening/ring-closing metathesis; and

Fig. 16 shows enantioselective desymmetrization of dienes by tandem Mo-catalyzed ring-opening/ring-closing metathesis.

## Detailed Description

The present invention provides, in one aspect, an olefin metathesis catalyst. In one illustrative embodiment of this aspect of the present invention, a composition is provided comprising the structure:



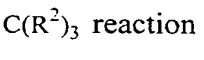
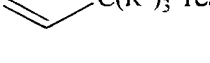
I

The metal ion, M, is preferably molybdenum or tungsten. The composition has a chiral dialkoxide, denoted by  . The term "chiral" herein refers to a molecule that is not superimposable with its mirror image. The resulting nonsuperimposable mirror images are known as "enantiomers" and are labeled as either an (R) enantiomer or an (S) enantiomer.

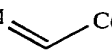
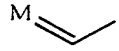
Because enantiomers contain chiral centers, they are included in a specific type of isomerism called "stereoisomerism." A molecule such as $CX_2WY$ would not have enantiomers; the replacement of one X by another group Z, however, would lead to one enantiomer: conversely the replacement of the other X by Z would lead to the other enantiomer. From this viewpoint, the X atoms in $CX_2WY$ are not equivalent and are defined as "enantiotopic". A "prochiral molecule" is a molecule such as $CX_2WY$ that contains two enantiotopic atoms or groups, such as the X atoms in $CX_2WY$.

$R^1$ and $R^2$ can be the same or different, and each is selected from the group consisting of $C_1$-$C_{12}$ alkyl, heteroalkyl, aryl, heteroaryl and adamantyl. Preferably, $R^1$ is 2,6-dimethylphenyl, 2,6-diethylphenyl or 2,6-diisopropylphenyl and $R^2$ is methyl, ethyl or phenyl.

An "alkoxide" ligand herein refers to a ligand prepared from an alcohol, in that removing the hydroxyl proton from an alcohol results in a negatively charged alkoxide. The alkoxide of the present invention is a linked, bidentate dialkoxide ligand. Moreover, the dialkoxide is chiral and can exist as one of two enantiomers. Each dialkoxide enantiomer interacts with plane-polarized light differently, in that this plane is rotated by both enantiomers to the same extent but in opposite directions. If a sample contains only one enantiomer, a measurement of the sample's optical activity would reveal an "optically pure" compound. The chiral dialkoxide of the present invention is of at least 80 % optical purity in that the dialkoxide sample contains 90 % of one enantiomer and 10 % of the other. The dialkoxide preferably is at least 90 % optically pure, more preferably at least 95 % optically pure, and more preferably still at least 99 % optically pure.

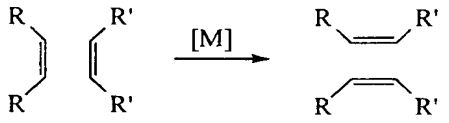
It is a feature of the present invention that a catalytic composition is provided having a dialkoxide of sufficient rigidity such that, in conjunction with an M=N-$R^1$ site, the combination of the dialkoxide and the M=N-$R^1$ site in part confers a shape specificity to a  reaction site where the composition reacts with an olefin. This shape specificity, imparted by rigidity of the dialkoxide ligand, is sufficient to allow a mixture of two enantiomeric olefins to react with a M=C center of the  reaction site at different rates. That is, the invention provides a catalyst designed to have shape specificity sufficient to differentiate between enantiomers of a reactant by sterically interacting with one enantiomer almost exclusively or exclusively. A means to achieve a preference for one enantiomer over the other, or enantiomeric selectivity, is kinetic resolution. Enantiomeric

selectivity by kinetic resolution involves steric interactions in the transition state of the reaction of the substrate at the catalyst such that the transition state involving one enantiomer is of lower energy than the transition state of the other enantiomer. Consequently, the term shape specificity in the present invention refers to the shape of an M=C reaction site in the transition state, as formed by the surrounding ligands, such that upon reaction of the substrate with the metal compound, one enantiomer "fits into" the binding site with less steric interaction than the other enantiomer. The transition state energy is lower for the enantiomer with a better "fit" or shape specificity over the other.

In another embodiment, the chiral dialkoxide of at least 80 % optical purity has sufficient rigidity such that a  reaction site is of sufficient shape specificity, defined in part by the dialkoxide and a M=N-R site, to cause a molecular substrate having a plane of symmetry to react with a M=C center at the  reaction site forming a catalytic olefin metathesis product that is free of a plane of symmetry. The product has at least a 50 % enantiomeric excess of at least one enantiomer present in the mixture.

A method to screen for dialkoxides having sufficient rigidity for shape specificity purposes involves obtaining an enantiomeric mixture of a test dialkoxide, isolating one enantiomer and measuring a specific rotation. A dialkoxide of sufficient rigidity would provide a specific rotation as opposed to reverting back to an enantiomeric mixture.

Generally, two enantiomeric olefins can react with an M=C center catalytically to form an olefin metathesis product. Olefin metathesis is defined conceptually as a mutual exchange of alkylidene units between two olefins, as illustrated in eq 1:




(1)

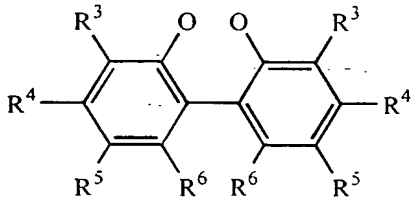
Although "olefin metathesis" generally refers to a reaction between two olefin or alkene groups, "olefin metathesis" is also used herein to refer to reactions involving at least one alkyne group. Thus, olefin metathesis reactions can occur between two triple bonded groups or between a double bonded and a triple bonded group.

Olefin metathesis can be catalyzed by a metal complex, denoted in the equation as [M]. In the present invention, the metal complex is a chiral metal complex including a chiral metal center that can transform olefin substrates (reactants) into optically pure products.

Typically, the substrate is a racemic mixture, the term "racemic" referring to a mixture containing an equal ratio of (R) and (S) enantiomers. The chiral metal complex of the invention can function as an asymmetric catalyst and simplifies the reaction process due to its ability to resolve a racemic mixture in generating a product of high enantioselectivity, or optical purity. The extent of optical purity of a product is gauged by the "enantiomeric excess" or "e.e." of the product mixture. The enantiomeric excess is the difference between the percent of the majority enantiomer minus the percent of the minority isomer, as represented by the equation [([R] - [S])/([R] + [S])] x 100 in which [R] and [S] refers to a concentration of the (R) and (S) enantiomer respectively. For example, if a mixture contains a 50 % e.e. of the (R) configuration, the mixture contains 75 % of the (R) configuration and 25 % of the (S) configuration. In the present invention, a mixture of the two enantiomeric olefins react with the M=C center at different rates to generate an olefin metathesis product that has at least a 50 % enantiomeric excess of one enantiomer present in the mixture, preferably at least 85 %, more preferably at least 90 % and more preferably still at least 95 %.

In one embodiment of the invention, a species as defined above is provided including a dialkoxide comprising two linked oxygen atoms such that the group of atoms defining the shortest chemical bond pathway between the two oxygen atoms has at least four atoms. For example, the four atoms can be four unsaturated atoms which confer rigidity to an organic group because they possess less degrees of freedom than a saturated atom. Examples of unsaturated carbon atoms are found in alkene, alkyne or aryl substituents.

The present invention also provides a dialkoxide, which can comprise  in **I**, comprising the structure:



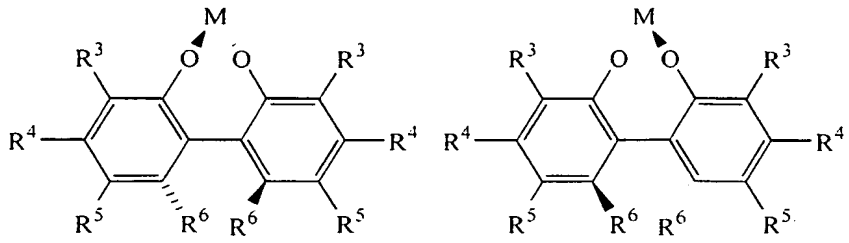
**II**

wherein $R^3$ - $R^6$ can be the same or different, and each is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, aralkyl, silyl and optionally interrupted or terminated by N, O, P, S, Si, heteroalkyl,

heteroaryl, carbonyl, acyl, acyloxy, —CHO, —$COOR^7$, —$CO_2C(R^7)_3$, —$CONC(R^7)_2$, cyano, $NO_2$, alkyloxy, aryloxy, hydroxy, hydroxyalkyl, amino, alkylamino, dialkylamino, arylamino, diarylamino, — $NR^7COR^8$, thioalkyl, thioaryl,—$SO_2R^7$, —$SOR^7$, —$SO_2OR^7$, F, Cl, Br, I; $R^7$ and $R^8$ can be the same or different, and each is selected from the group consisting of hydrogen, $C_1$-$C_{12}$ alkyl, $C_1$-$C_{12}$ heteroalkyl, aryl, heteroaryl, hydroxyl, F, Cl, Br and I; and any two R groups where possible can combine to form a closed ring system selected from the group consisting of aryl, heteroaryl, substituted aryl, biaryls, and substituted biaryls. Preferably, $R^3$ - $R^6$ can be the same or different and each is selected from the group consisting of $C_1$-$C_{12}$ alkyl, heteroalkyl, aryl, heteroaryl, optionally interrupted or terminated by N or O, and any two R groups where possible can combine to form a closed ring system selected from the group consisting of aryl, heteroaryl, substituted aryl, biaryls and substituted biaryls. More preferably, $R^3$ is i-propyl, t-butyl, cyclohexyl, t-octyl, $R^4$ is hydrogen or $C_1$-$C_2$ alkyl, $R^5$ is hydrogen or $C_1$-$C_2$ alkyl, and $R^6$ is methyl.

Fig. 2 shows example catalysts of the present invention where NR comprises a substituted aryl group. $R^1$ - $R^4$ can be the same or different and each is selected from the group consisting of hydrogen, alkyls, aryls, alkaryls and substituted derivatives thereof. In one embodiment, $R^3$ comprises bulky substituents. For example, $R^3$ can be selected from the group consisting of ethyl, *i*-Pr, *t*-Bu, 2,4,6-tri(*i*-propyl)phenyl, phenyl and adamantyl. In one embodiment, $R^1$ and $R^2$ are selected from the group consisting of i-Pr and methyl. $R^1$ and $R^2$ can be different; for example $R^1$ can be $CF_3$ and $R^2$ can be hydrogen. In one embodiment, $R^4$ is selected from the group consisting of hydrogen and $^t$-Bu. The catalysts of the present invention can also comprise additional ligands, such as a tetrahydrofuran ligand, as shown in catalyst **2**.

The chirality of the dialkoxide according to this embodiment results from steric interactions of the $R^6$ groups maintaining a rotational orientation of the phenyl groups about the biaryl bond such that the two phenyl groups are non-planar with respect to each other. In this manner, the dialkoxide of this embodiment confers chirality to a metal complex, as illustrated below:



IV V

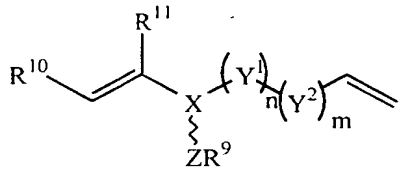
In a particularly preferred embodiment, the dialkoxide of the invention confers chirality to the metal complexes **IV** and **V** through the interaction between $R^6$ methyl groups of dialkoxide **II**. The present invention provides a composition that is a chiral metal complex in which the composition is at least 80 % optically pure, preferably at least 90 % optically pure, more preferably at least 95 % optically pure, and more preferably still at least 99 % optically pure.

While not wishing to be bound by any theory, specificity of the catalyst of the invention where the alkoxide is **II** is due to the following: Upon binding the dialkoxide to a metal center, a seven-membered metallacycle results. This configuration allows bulky functional groups in the $R^3$ positions to point towards the general direction of the M=C reaction center, aiding in providing shape specificity to the M=C reaction site.

In another embodiment of the present invention, the olefin metathesis reaction is a ring-closing metathesis (RCM) reaction in which a ring-closed compound is produced. Preferably, the ring-closed compound is a cyclic olefin. To obtain the cyclic product, the substrate contains at least two points of unsaturation (e.g. a diene or triene) to achieve ring-closing through two subsequent olefin metathesis reactions. The diene source of the present invention is a racemic diene mixture where the diene is of from about 4 to about 18 carbons in length, preferably from about 7 to about 12 carbons in length. The double bonds of the diene are separated by enough distance that a ring can be formed. Other considerations for diene selection are described below. Exposing the composition of the present invention to the racemic diene mixture produces a ring-closed compound with high enantioselectivity. This high enantioselectivity is demonstrated at 50 % conversion of the racemic diene mixture, in which the ring-closed compound has an enantiomeric excess of at least 50 %, preferably at least 85 %, more preferably at least 90 % and more preferably still at least 95 %. The enantiomeric excess of the remaining unreacted diene can also be measured. At 50 % conversion of the racemic diene mixture, the unreacted diene has an enantiomeric excess of at least 50 %, more preferably at least 85 %.

Another aspect of the invention provides a method comprising reacting the composition, **I**, of the present invention with a diene. In one embodiment of this aspect of the invention, the method comprises reacting an enantiomeric diene mixture with the composition of the present invention and allowing a first enantiomer of the mixture to metathesize at the metal ion, M, to an extent greater than a second enantiomer of the mixture. The resulting product has an enantiomeric excess of at least 50.%. The composition is at least 80 % optically pure, preferably at least 90 % optically pure, more preferably at least 95 % optically pure and more preferably still 99 % optically pure. Preferably, the metal ion is molybdenum or tungsten.

In another embodiment of the invention, addition of the diene mixture to the compound produces a ring-closed compound. Preferably the ring-closing reaction is a ring-closing metathesis reaction. In this embodiment the enantiomeric diene mixture of the present invention comprises the structure:



**III**

The method of reacting the diene with the composition can optionally include the step of dissolving the composition in a solvent before adding the diene.

The extent of substitution on the respective diene olefinic groups can be important in preventing undesirable side reactions which would decrease metathesis activity and product selectivity. Due to steric demands, an unsubstituted olefin reacts with an M=C bond at a faster rate than a substituted olefin. A diene containing two terminal unsubstituted olefin groups, however, will react with M=C reaction sites to generate polymers and dimers by the well-known acyclic diene metathesis reaction. If desirable, the rate of metathesis can be decreased to the extent that polymer formation is negligible typically by substituting the hydrogen atoms on the second olefin group with bulkier substituents such as methyl, ethyl, or the like, for example the $R^{10}$ or $R^{11}$ groups in the above-mentioned structure.

Referring to Fig. 1, a proposed mechanism for an RCM catalytic cycle involving diene **III** is shown, illustrating the reasons for the preferred diene structure according to this embodiment. At the top of Fig. 1, a complex containing a M=C reaction site reacts with a

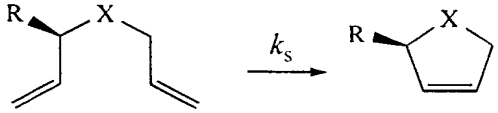
diene structure of the present invention at the unsubstituted terminal olefin site. A metallacyclobutane intermediate results that subsequently releases an olefin and a metal complex containing the reacted diene group. This complex can either react with the substituted olefin intramolecularly or with another diene intermolecularly at its unsubstituted terminal olefin site. The latter reaction is unproductive with respect to ring-closed product formation, however, in that the resulting product dimer is unstable and upon reaction with a M=C reaction site, reverts back to the M=C complex. The intramolecular reaction produces a bicyclic compound comprising a metallacyclobutane fused to another closed-ring structure which consequently transforms into cyclic olefin product and a complex containing a M=C reaction site. Yet another undesirable side reaction is metathesis of the cyclic olefin product with the M=C reaction site through a ring-opening metathesis process. Again, designing the diene to produce a cyclic olefin that affords minimal ring strain or that contains a relatively hindered olefin may contribute to a decrease in rate of the ring-opening reaction.

In embodiments of the present invention in which the diene is **III**, X is selected from the group consisting of $CR^{12}$, N or P. $Y^1$, $Y^2$ and Z can be the same or different and each is selected from the group consisting of $CR^{12}R^{13}$, $NR^{12}$, O or S. When a diene contains main group elements at the X, $Y^1$ or $Y^2$ sites, heterocyclic products can be formed. $R^{10}$ and $R^{11}$ can be the same or different, and each is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, aralkyl and optionally interrupted or terminated by N, O, P, S, heteroalkyl, heteroaryl, carbonyl, acyl, acyloxy, —CHO, —$COOR^{12}$, —$CO_2C(R^{12})_3$, —$CONC(R^{12})_2$, cyano, $NO_2$, alkyloxy, aryloxy, hydroxy, hydroxyalkyl, amino, alkylamino, dialkylamino, arylamino, diarylamino, — $NR^{12}COR^{13}$, thioalkyl, thioaryl, —$SO_2R^{12}$, —$SOR^{12}$, —$SO_2OR^{12}$, F, Cl, Br, I. $R^9$, $R^{12}$ and $R^{13}$ can be the same or different, and each is selected from the group consisting of hydrogen, $C_1$ -$C_{12}$ alkyl, $C_1$-$C_{12}$ heteroalkyl, aryl, heteroaryl, hydroxyl, alkylsilyl, arylsilyl, alkarylsilyl, F, Cl, Br and I. Any two R groups, where possible, can combine to form a closed ring system selected from the group consisting of aryl, heteroaryl, substituted aryl, biaryls, and substituted biaryls. The value "n+m" is at least 2. Preferably, n+m ranges from 2 to 4. More preferably, n+m = 2. Where n+m = 2, the cyclic product is a five-membered ring. Increasing n or m provides for the possibility of forming larger ring systems. Preferably, $Y^1$, $Y^2$ and Z can be the same or different and each is selected from the group consisting of $CR^{12}R^{13}$, $NR^{12}$, O or S. $R^{10}$, $R^{11}$, $R^{12}$, and $R^{13}$ can be the same or different and each is selected from the group consisting of $C_1$-

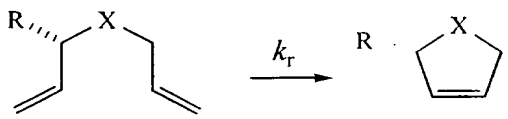
$C_{12}$ alkyl, heteroalkyl, aryl or substituted aryl and $R^9$ is selected from the group consisting $C_1$-$C_{12}$ alkyl, heteroalkyl, aryl or substituted aryl, alkylsilyl, arylsilyl, and alkylarylsilyl. More preferably, X is CH, $Y^1$ and $Y^2$ each are $CH_2$, and $ZR^9$ is selected from the group consisting of acetate, t-butylacetate, trifluoroacetate, and trialkylsilyloxide.

In another embodiment of the invention, a method is provided that generates a ring-closed metathesis compound from a racemic diene mixture such that at 50 % conversion of the racemic diene mixture, the product has an enantiomeric excess of at least 50 %, preferably 85 %, more preferably at least 90 % and more preferably still at least 95 %. The optical purity of the unreacted diene can also be analyzed and at 50 % conversion of the racemic diene mixture, the enantiomeric excess of the unreacted diene is at least 50 %, preferably at least 85 %. In another embodiment of the invention, a step of adding the diene mixture to the composition results in 50 % conversion of the racemic diene mixture almost immediately, e.g. within at least 1 second. Of course, other reactions may take longer periods of time from at least 5 min to several hours.

The present invention also provides a method to achieve enantiomeric selectivity through kinetic resolution. As discussed previously, kinetic resolution can be achieved when a transition state involving the reaction of the M=C center with one enantiomer is of lower energy than a transition state involving the other enantiomer. This lowered transition state energy arises from the shape specificity of the binding site for that one particular enantiomer, the end result being that the one enantiomer undergoes RCM at a faster rate than the other enantiomer. The reaction rate is dependent on the rate constant, in which the rate constant of a reaction involving the (S) enantiomer is labeled as $k_s$, and the rate constant of a reaction involving the (R) enantiomer is denoted by $k_r$, in equations 2 and 3, respectively. For example, to obtain a product mixture containing predominantly the (R) enantiomer, $k_r$ should be sufficiently greater than $k_s$. The present invention provides sufficient kinetic resolution to obtain, for example, the (R) enantiomer of the product such that adequate optical purity, as defined above, is achieved when the value of $\mathbf{S} = k_r/k_s$ (eq 4) is at least 10, preferably at least 25.




(2)



(3)

$$\text{Relative Rate} = S = k_r/k_s \quad (4)$$

In one embodiment, the method allows for the preparation of enantiomerically enriched heterocycles. This method involves the kinetic resolution of acyclic dienes that contain a heteroatom within the cyclizing chain.

Another aspect of the present invention provides a method for performing kinetic resolution. The method involves providing at least one substrate having at least one olefin group. The method also involves selecting a catalyst of sufficient steric bulk to initiate an olefin metathesis reaction involving the at least one substrate to achieve a $k_{rel}$ of at least about 10, more preferably at least about 20. "Selecting a catalyst" refers to the ability to tune the catalyst by varying the appropriate groups such that high efficiency is achieved.

In one embodiment, the method involves one substrate having two olefin groups. In another embodiment, the method involve two substrates, each substrate having at least one olefin group. In one embodiment, the reaction is selected from the group consisting of a ring-opening metathesis reaction, a cross-metathesis reaction and a ring-closing metathesis reaction.

An example of selecting a catalyst is demonstrated here. FIG. 3 shows a scheme for ring-closing substrate 3. As shown in the Examples section and referring to FIG. 2, under these conditions, catalyst **1a** promotes ring-closure with high enantiodifferentiation whereas catalyst **2a** ring-closes with significantly reduced selectivity. Catalyst **2b** effects RCM without any discrimination between the diene enantiomers.

FIG. 4 shows a scheme for asymmetric RCM to form 6-membered rings from a 1,7-diene substrate. Referring to accompanying Table 1, it can be seen that this time, catalyst **2a** shows superior enantioselectivity whereas catalyst 1a results in significantly less enantiodifferentiation.

FIG. 5 shows substrates for asymmetric RCM to form 6-membered rings including a heteroatom. Referring to accompanying Table 2, it can be seen that catalyst **2a** effects highly efficient kinetic resolutions for substrates 57 and 59 in contrast with catalyst **1a**, which provides substantial amounts of dimer and negligible enantiodifferentiation. Catalyst **1b**

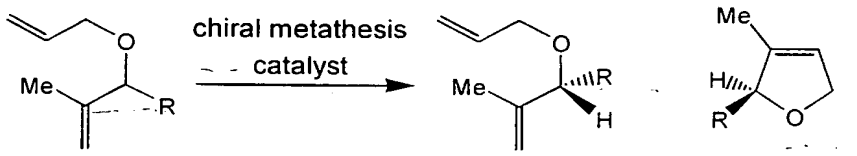
produces a higher kinetic resolution efficiency over catalyst **1a** but substantially lower values than those for catalyst **2a**. While not wishing to be bound by any theory, this difference may be attributed to a presence of sterically bulky dimethylsilyl groups in these substrates inhibiting association of two substrate molecules with the chiral transition metal center of catalyst **2a**.

For substrates 61 and 63, however, where both reactive sites comprise terminal olefins, catalyst **1a** effects the highest enantiodifferentiations. Again, not wishing to be bound by any theory, it appears that catalyst **1a** is the preferred selected catalyst for substrates having two terminal alkenes whereas catalyst **2a** is a superior catalyst for reactions that involve highly substituted alkenes.

Another aspect of the invention provides a method for catalytic, enantioselective desymmetrization. Desymmetrization reactions involve the transformation of a molecular substrate, i.e. reactant, having a plane of symmetry into a product free of a plane of symmetry where the transformation involves two reactive sites situated on the substrate. For example, the desymmetrization reaction can be a carbon-carbon bond forming reaction such as olefin metathesis involving at least two reactive sites. Where only one substrate is involved in the desymmetrization reaction, the olefin metathesis may be a ring-closing metathesis and/or a ring-opening metathesis reaction. In another embodiment, two molecular substrates may be involved in the desymmetrization, such as in a cross-metathesis reaction between a first molecular substrate and a second molecular substrate.

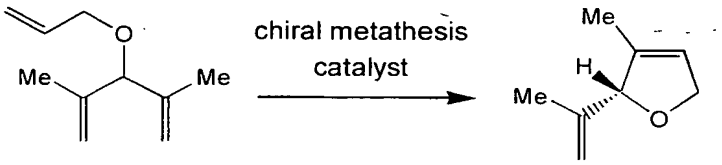
By removing the plane of symmetry in the substrate i.e. a substrate free of a plane of symmetry, preferably the product possesses a stereocenter. Thus in asymmetric synthesis, an advantage of enantioselective desymmetrization over kinetic resolution is the ability to produce optically active products in high yields of up to 100%. Where a product can only be made from a substrate comprising a racemic mixture of enantiomers that are not easily isolated or kinetically resolved, enantioselective desymmetrization may eliminate the need for purification or kinetic resolution. The distinction between kinetic resolution and enantioselective desymmetrization can be illustrated by the examples shown in equations 5 and 6:

**Catalytic Kinetic Resolution** (5)




*racemic* *non-racemic* *non-racemic*

**Catalytic Enantioselective Desymmetrization**




(6)

*achiral* *chiral, non-racemic*

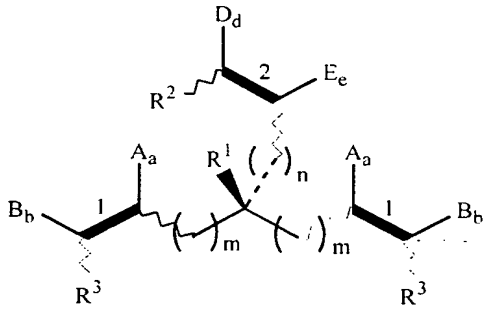
The desymmetrization reaction can be initiated by the addition of a catalyst, resulting in a catalytic desymmetrization reaction. In one embodiment, at a turnover number of at least about 2 and preferably at least about 5, at least one enantiomer of a product is formed in an enantiomeric excess of at least about 20%. "Turnover number" reflects catalyst efficiency and robustness. For example, sufficiently active catalysts can result in high reaction rates, which can translate into high turnover numbers. High turnover numbers are also achieved where catalysts are robust and sufficiently withstand decomposition. Consequently, robust catalysts can maintain the integrity of the catalyst structure and function over long periods of time. Preferably, the turnover number is at least about 10, more preferably at least about 25, more preferably still at least about 50 and more preferably still at least about 100. An advantageous feature of catalysts that produce high turnover numbers is that relatively low amounts of catalyst are required in the reaction mixture. Catalyst amounts are expressed in mol% relative to an amount of substrate. In a preferred embodiment, the catalyst can be present in an amount of less than about 15 mol%, preferably less than about 10 mol%, more preferably less than about 5 mol% and more preferably still less than about 1 mol%. Preferably, one enantiomer is formed in an enantiomeric excess of at least about 50%, preferably at least about 85%, more preferably at least about 90%, still more preferably at least about 95% and still more preferably at least about 99%. In another embodiment, two enantiomers are formed in an enantiomeric excess of at least about 50%, preferably at least about 85%, more preferably at least about 90%, still more preferably at least about 95% and

still more preferably at least about 99%.

The catalyst can be a metal complex. In one embodiment, the metal complex is a transition metal complex including at least one metal-carbon double bond. In this embodiment, the metal-carbon double bond can initiate an olefin metathesis reaction with the substrate. In another embodiment, the metal complex is a transition metal dialkoxide complex. In yet another embodiment, the transition metal dialkoxide complex comprises the structure **I**, as discussed previously.

In another embodiment, the molecular substrate can be selected from the group consisting of achiral and meso substrates. An "achiral" molecule is superimposable on its mirror image. Although a "meso" substrate possesses at least two chiral centers, this substrate also has a plane of symmetry, rendering meso substrates optically inactive. Both the substrate and product can be either cyclic or acyclic.

In one embodiment, the molecular substrate comprises a structure:



**VI**

The substrate possesses a plane of symmetry, in accordance with the present invention. In **VI**, A, B, D, E and $R^1$ - $R^3$ can be the same or different and each of A, B, D, E and $R^1$ - $R^3$ is selected from the group consisting of hydrogen, hydroxy, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl are hydrocarbons optionally interrupted by a functional group including at least one non-carbon element. A "functional group including at least one non-carbon element" can include any one of a main group element, transition metal, lanthanide, actinide, a main group element containing substituent, transition metal containing substituent, lanthanide containing substituent, or an actinide containing substituent. For example, the functional group including a non-carbon element can be a metal ion or a metal-containing substituent having a number of ligands, the number of ligands being dictated by the ligand-type, ligand charge and a charge on the metal. The functional group can also be any main group element or a main

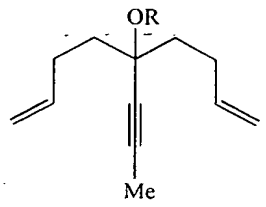
group element appended to a number of substituents, the number being dictated by the elemental charge, the substituent-type and the charge on the substituent. In another embodiment, the functional group including at least one non-carbon element is selected from the group consisting of O, S, Se, silane, silyl ether, carbonyl, carboxyl, carboxylate, ether, ester, anhydride, acyl, cyano, $NO_2$, alkyloxy, aryloxy, hydroxy, hydroxyalkyl, amino, alkylamino, arylamino, amido, thioalkyl, thioaryl, sulfonate, phosphate, phosphonate, phosphane and stannane. The functional group can be reactive or nonreactive.

The symbol "┃" denotes either a double bond or a triple bond. In **VI**, "1┃" and "2┃" can be the same or different and each of "1┃" and "2┃" can be either a double or a triple bond. The bonds denoted by the symbol "〰" do not necessarily conform to the geometry shown in the above structure. -a, b, d, and e can be the same or different and each of a, b, d and e is an integer equaling 0 to 1. For example in the above structure, when "1┃" is a triple bond, a and b are zero, and the bonds to substituents A and B are eliminated. In this situation, at least the first atom of $R^3$, both carbon atoms of the triple bond and the adjacent carbon (bound to $R^1$) are arranged in an essentially linear fashion, as required by the sp hybridization of the carbon atoms of "1┃". When "1┃" is a double bond, a and b are equal to 1, the carbon atoms of the double bond are $sp^2$ hybridized and the substituents around "1┃" have a geometry approximated as shown by the above structure.

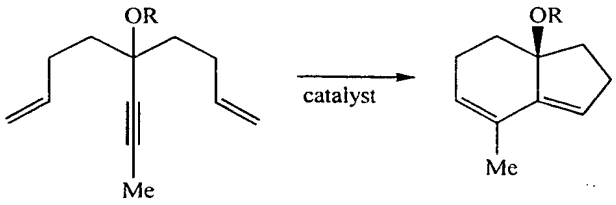
Either of "1┃" and "2┃" are reactive sites. For example, either of "1┃" and "2┃" can be involved in an olefin metathesis reaction. Metathesis can occur between both "1┃" groups or between one "1┃" group and a "2┃" group. The method of the present invention provides metathesis reactions involving different combinations of double and triple bonded groups. For example, both "1┃" and "2┃" can be a double bond and a reaction involving one "1┃" group and "2┃" can result to form an alkene/alkene metathesis product; both "1┃" and "2┃" can be a triple bond and a reaction involving one "1┃" group and "2┃" can result to form an alkyne/alkyne metathesis product; or "1┃" can be a triple bond and "2┃" can be a double bond or vice versa and a reaction involving one "1┃" group and "2┃" can result to form an alkyne/alkene metathesis product. Similar alkene/alkene and alkyne/alkyne combination reactions can also occur between both "1┃" groups. A substrate possessing an alkyne unit also has the potential to participate in at least two ring-closing metathesis reactions. For example, when an alkyne is involved in a first metathesis reaction, an alkene results which may participate in a subsequent second metathesis reaction.

In a preferred embodiment, the molecular substrate is involved in a ring-closing metathesis reaction, causing the formation of a cyclic structure. In the above structure, m and n are integers which can be the same and each of m and n are integers preferably equaling 0-20. The indices m and n represent a number of $-CH_2-$ linker units in the substrate. Controlling the value of m and n in the substrate can allow control of the ring size in the resulting product. In another embodiment, m and n equal 0-10. In one embodiment, the product includes at least one ring having a ring size of less than about 20 atoms and preferably the ring size is less than about 10 atoms.

A non-limiting example of a molecular substrate comprises a structure:

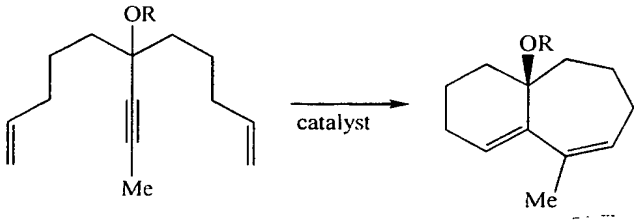



In this example, m=2, n=0, both "1" groups are double bonds and "2" is a triple bond. The catalyst can initiate a metathesis reaction with either the double bond or the triple bond of the substrate. In addition, there are two possible alignment orientations of the metal-carbon double bond of the catalyst with either a double or triple bond of the substrate immediately prior to metathesis. A resulting intermediate and the subsequent product can thus have various geometrical isomers. One example of a ring-closed product is shown in eq 7:




(7)

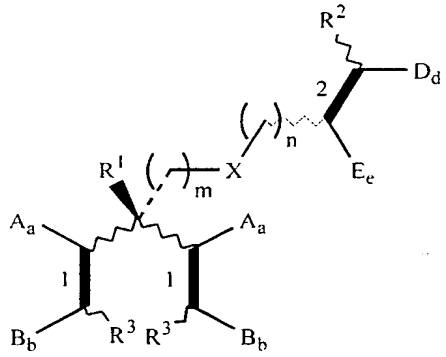
Equation 7 shows a bicyclic structure comprising fused closed-ring systems, specifically a fused five- and six-membered ring structure. The ring size can be varied by changing a number of $-CH_2-$ of the substrate. One example of this variation in ring size is shown in eq 8 where m=3:




(8)

In this example, a fused six- and seven-membered ring structure is produced.

In another embodiment, the molecular substrate comprises a structure:

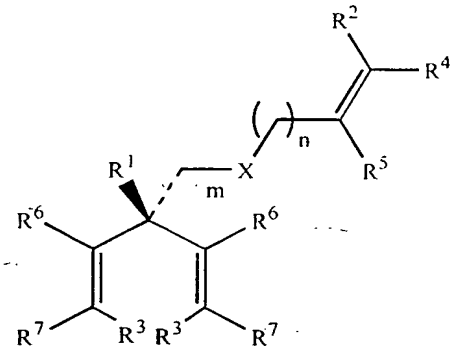



**VII**

In **VII**, "1 ▌" and "2▌" can be the same or different and each of "1 ▌" and "2▌" denotes a bond selected from the group consisting of a double bond and a triple bond. This structure includes "X", where X can be a functional substituent. A "functional substituent" as used herein can include any one of a main group element, transition metal, lanthanide, actinide, a main group element containing substituent, transition metal containing substituent, lanthanide containing substituent, an actinide containing substituent, or a saturated or unsaturated hydrocarbon $C_xH_y$ group, where x and y are at least 1. For example, the functional substituent can be a metal ion or a metal-containing substituent having a number of ligands, the number of ligands being dictated by the ligand-type, ligand charge and a charge on the metal. The functional substituent can also be any main group element or a main group element appended to a number of substituents, the number being dictated by the elemental charge, the substituent-type and the charge on the substituent. When "2▌" is involved in a ring-closing metathesis reaction, the product can include a heterocyclic ring. In one embodiment, X can be selected from the group consisting of $CR^8R^9$, carbonyl, ester, $SiR^8R^9$, $OSi(R^8)(R^9)$, $SnR^8R^9$, O, S, Se, $NR^8$, $PR^8$, and $PO_3R^8$. $R^8$ and $R^9$ can be the same or different and each of $R^8$ and $R^9$ is selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl.

In **VII**, A, B, D, E and $R^1$ - $R^3$ can be the same or different and each of A, B, D, E and $R^1$ - $R^3$ can be selected from the group consisting of hydrogen, hydroxy, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. In all embodiments for **VII**, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl are hydrocarbons optionally interrupted by a functional group including at least one non-carbon element. In one embodiment, the functional group including at least one non-carbon element is selected from the group consisting of O, S, Se, silane, silyl ether, carbonyl, carboxyl, carboxylate, ether, ester, anhydride, acyl, cyano, $NO_2$, alkyloxy, aryloxy, hydroxy, hydroxyalkyl, amino, alkylamino, arylamino, amido, thioalkyl, thioaryl, sulfonate, phosphate, phosphonate, phosphane and stannane. In **VII**, a, b, d, and e can be the same or different and each of a, b, d and e is an integer equaling 0 to 1. m and n can be the same or different and each of m and n are integers preferably equaling 0-20, and more preferably equaling 0-10.

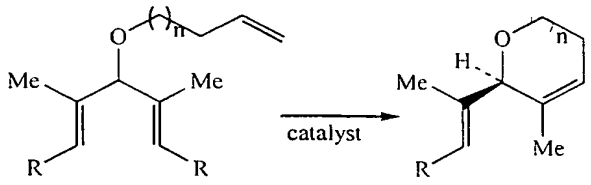
In another embodiment, the molecular substrate comprises a structure:



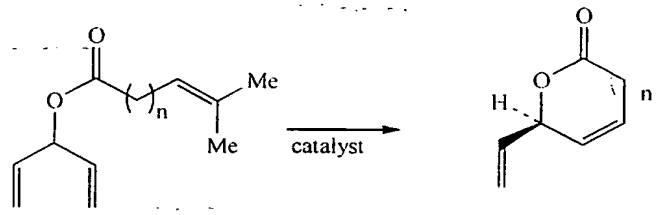
**VIII**

**VIII** is related to **VII** in that "1 ▌" and "2▌" of **VII** both represent double bonds and accordingly, a, b, d and e all equal 1. As discussed previously, any combination of double bonds can undergo an alkene/alkene metathesis reaction to form a cyclic structure. In a preferred embodiment, the product comprises a heterocycle including X. $R^1$ - $R^3$, m and n are defined as in **VII**. In **VIII**, $R^4$ - $R^7$ can be the same or different and each of $R^4$ - $R^7$ is selected from the group consisting of hydrogen, hydroxy, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl.

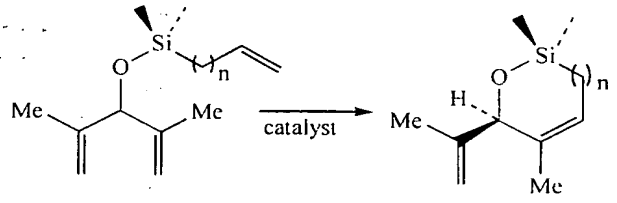
Examples of enantioselective desymmetrization reactions are illustrated in eqs 9 - 11:




(9)

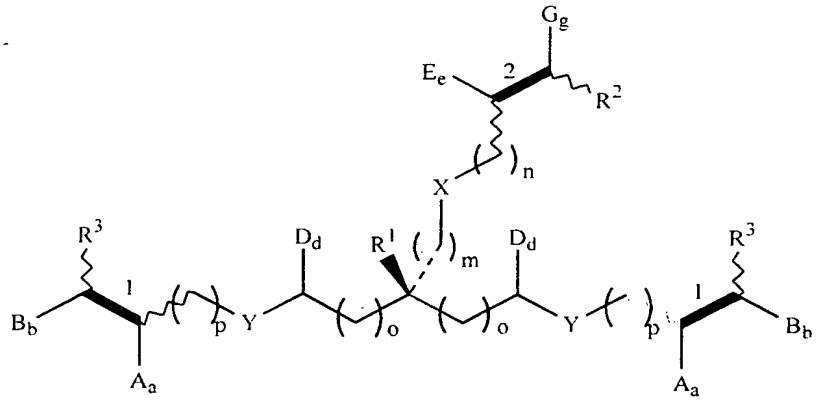



(10)




(11)

In another embodiment, the molecular substrate comprises a structure:



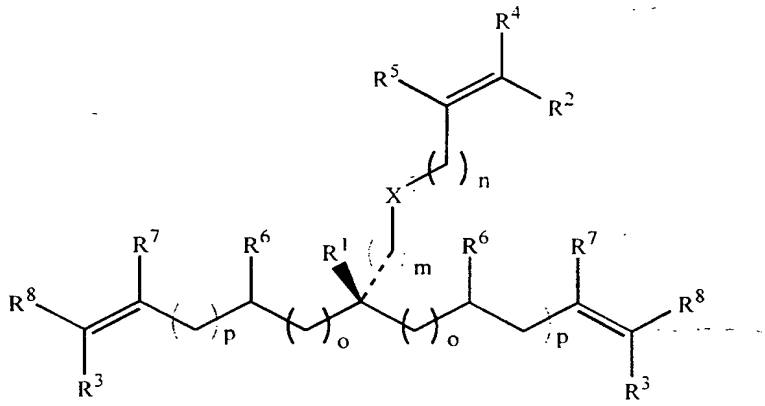

**IX**

When d=1 and D is a non-hydrogen element, **IX** represents a class of meso substrates. As discussed previously, although **IX** possesses two chiral centers, i.e. the carbon atoms bonded to $D_d$, the plane of symmetry renders this substrate optically inactive. **IX** can result in heterocyclic ring structures of various ring sizes. Y can be the same or different from X and can include any of the substituents listed for X.

In **IX**, "1 ▌" and "2▌" can be the same or different and each of "1 ▌" and "2▌" denotes a bond which can be selected from the group consisting of a double bond and a triple bond. As discussed previously, a metathesis reaction can occur between any combination of "1▌" and "2▌" along with double and triple bond combinations. a, b, d, e and g can be the same or different and each of a, b, d, e and g are integers equaling 0 to 1. m, n, o and p can be the same or different and each of m, n, o and p are integers preferably equaling 0-20, and more

preferably equaling 0-10. A, B, D, E, G and $R^1$ - $R^3$ can be the same or different and each of A, B, D, E, G and $R^1$ - $R^3$ is selected from the group consisting of hydrogen, hydroxy, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. X or Y can be a functional substituent. In another embodiment, X or Y can be selected from the group consisting of $CR^9R^{10}$, carbonyl, ester, $SiR^9R^{10}$, $OSi(R^9)(R^{10})$, $SnR^9R^{10}$, B, O, S, Se, $NR^9$, $PR^9$ and $PO_3R^9$. $R^9$ and $R^{10}$ can be selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. In all embodiments of **IX**, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl are hydrocarbons optionally interrupted by a functional group including at least one non-carbon element. In one embodiments, the functional group including at least one non-carbon element can be selected from the group consisting of O, S, Se, silane, silyl ether, carbonyl, carboxyl, carboxylate, ether, ester, anhydride, acyl, cyano, $NO_2$, alkyloxy, aryloxy, hydroxy, hydroxyalkyl, amino, alkylamino, arylamino, amido, thioalkyl, thioaryl, sulfonate, phosphate, phosphonate, phosphane and stannane.

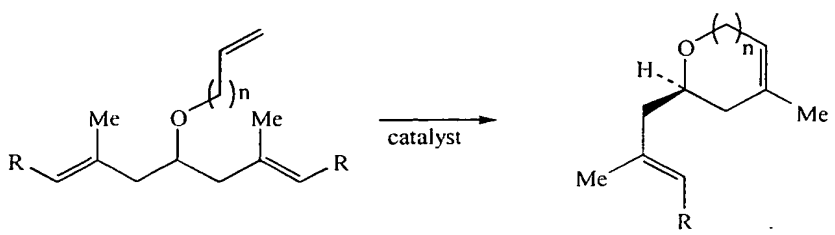
In another embodiment, the molecular substrate comprises a structure:



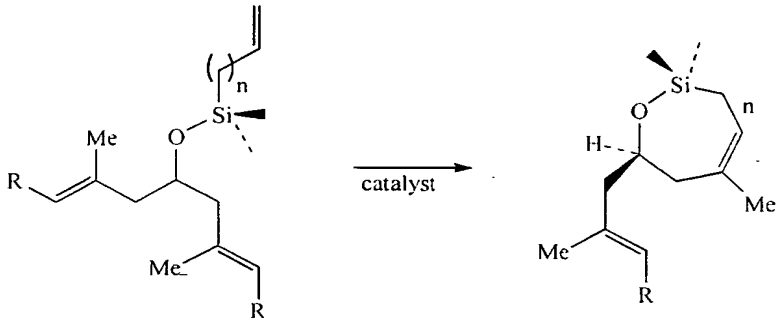
**X**

**X** is related to **IX** in that each of "1 ▌" and "2▌" represent double bonds and accordingly, each of a, b, d, e and g equal 1. $R^1$ - $R^3$, X, m, n, o and p are as defined for **IX**. In **X**, $R^4$ - $R^8$ can be the same or different and each of $R^4$ - $R^8$ is selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl are hydrocarbons optionally interrupted by a functional group including at least one non-carbon element.

Non-limiting examples of enantioselective metathesis reactions involving compounds in accordance with substrate **X** are illustrated in eqs 12 and 13:

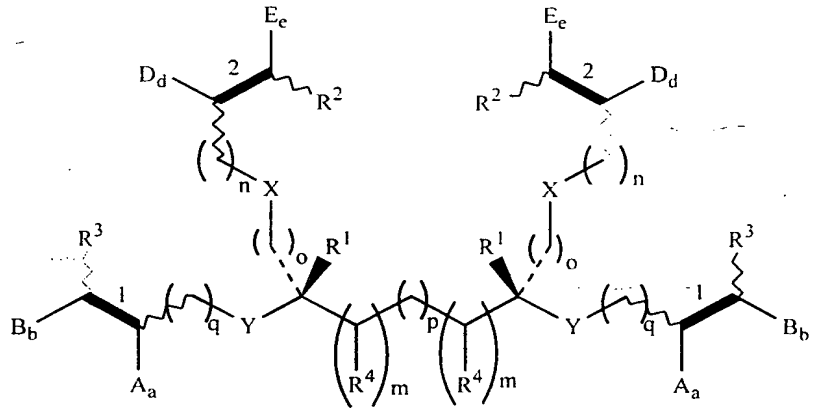



(12)




(13)

In another embodiment, the molecular substrate comprises a structure:

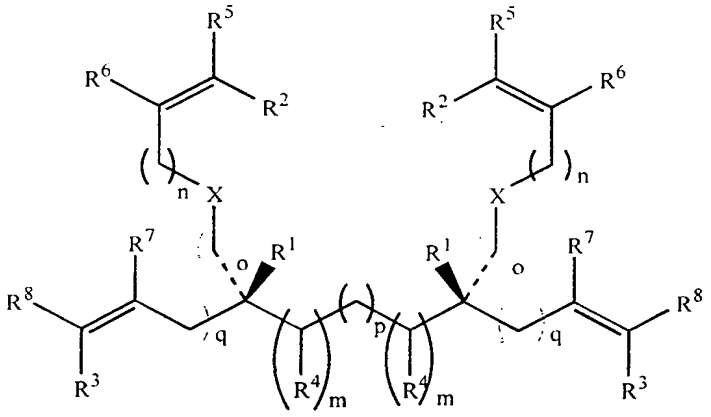



**XI**

The substrate **XI** represents another class of meso substrates. In **XI**, "1 ┃" and "2┃" can be the same or different and each of "1 ┃" and "2┃" denotes a bond selected from the group consisting of a double bond and a triple bond. X and Y can be the same or different and each can be a functional substituent. In another embodiment, X or Y can be selected from the group consisting of $CR^9R^{10}$, carbonyl, ester, $SiR^9R^{10}$, $OSi(R^9)(R^{10})$, $SnR^9R^{10}$, B, O, S, Se, $NR^9$, $PR^9$ and $PO_3R^9$. $R^9$ and $R^{10}$ can be the same or different and each of $R^9$ and $R^{10}$ is selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. a, b, d and e can be the same or different and each of a, b, d and e are integers equaling 0 to 1. m, n, o, p and q can be the same or different and each of m, n, o, p and q are

integers preferably equaling 0-20, and more preferably equaling 0-10. A, B, D, E and $R^1$ - $R^4$ can be the same or different and each of A, B, D, E and $R^1$ - $R^4$ is selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. In all embodiments for **XI**, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl are hydrocarbons optionally interrupted by a functional group including at least one non-carbon element. In one embodiment, the functional group including at least one non-carbon element is selected from the group consisting of O, S, Se, silane, silyl ether, carbonyl, carboxyl, carboxylate, ether, ester, anhydride, acyl, cyano, $NO_2$, alkyloxy, aryloxy, hydroxy, hydroxyalkyl, amino, alkylamino, arylamino, amido, thioalkyl, thioaryl, sulfonate, phosphate, phosphonate, phosphane and stannane.

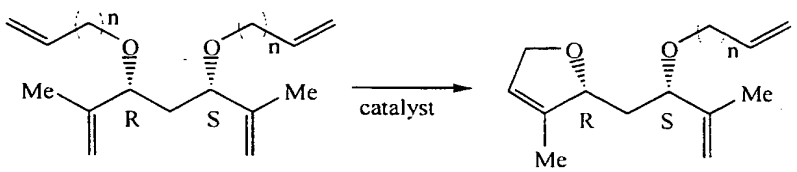
In another embodiment, the molecular substrate comprises a structure:



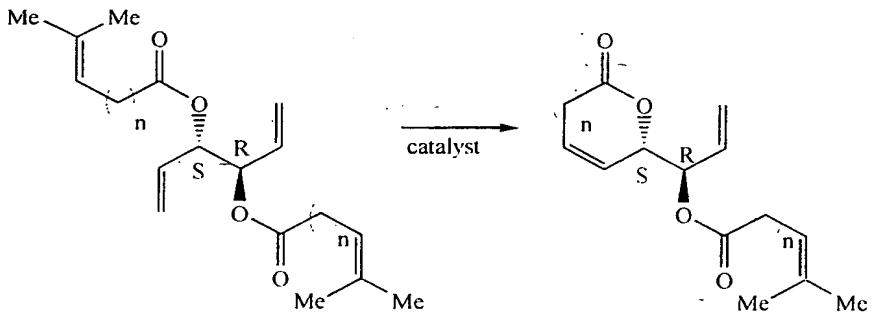
**XII**

**XII** is related to **XI**, in that each of "1 ▌" and "2▌" represent double bonds and each of a, b, d and e equal 1. $R^1$ - $R^4$, X, m, n, o, p and q are as defined for **XI**. In **XII**, $R^5$ - $R^8$ can be the same or different and each of $R^5$ - $R^8$ is a selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl, wherein $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl are hydrocarbons optionally interrupted a functional group including at least one non-carbon element.

Non-limiting examples of enantioselective metathesis reactions involving meso substrates are illustrated in eqs 14 and 15:



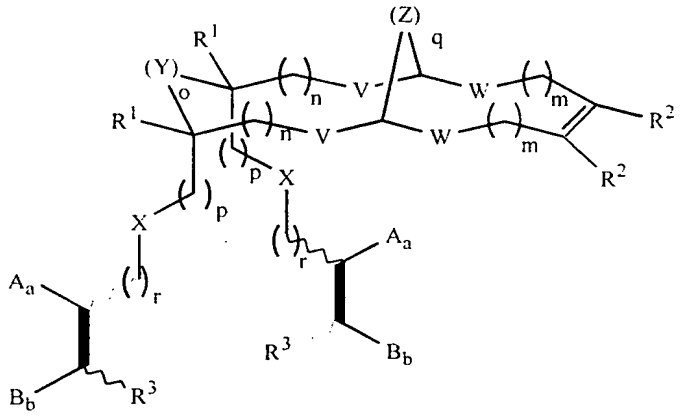

(14)




(15)

In one embodiment, the method provides for desymmetrization of trienes or tetraenes. Referring to FIG. 6 and Table 3, catalyst **1b** effectively inititates RCM of substrate 15 whereas catalyst **2a** promotes conversion of substrate 17 to a 6-membered ring species.

In another embodiment, the molecular substrate comprises a structure:




**XIII**

The substrate **XIII** can undergo a ring-opening metathesis reaction, where the catalyst initiates a metathesis reaction with the double bond of the substrate ring. **XIII** can also allow the formation of various fused-ring structures. " | " denotes a bond selected from the group consisting of a double bond and a triple bond. V, W, X, Y and Z can be the same or different and V, W, X, Y and X can be any functional substituent. In another embodiment, each of V, W, X, Y and Z is selected from the group consisting of $CR^6R^7$, carbonyl, ester, $SiR^6R^7$, $OSi(R^6)(R^7)$, $SnR^6R^7$, B, O, S, Se, $NR^6$, $PR^6$ and $PO_3R^6$. $R^6$ and $R^7$ can be the same or different and each of $R^6$ and $R^7$ is selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. a and b can be the same or different and each of a and b are integers equaling 0 to 1. m, n, o, p, q and r can be the same or different and each of m, n, o, p, q and r are integers preferably equaling 0-20, and more preferably equaling 0-10. A, B and $R^1$ - $R^3$ can be the same or different and each of A, B and $R^1$ - $R^3$ is selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl. $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and

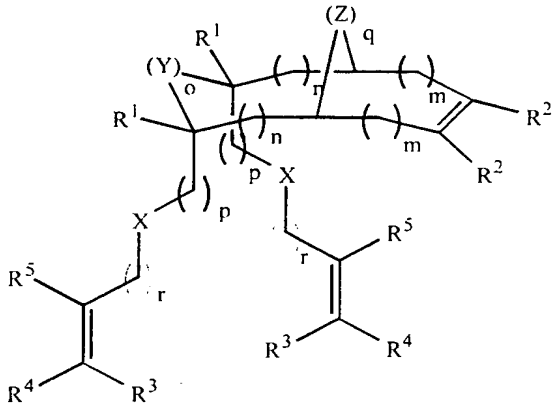
$C_1$-$C_{20}$ alkynyl. In all embodiments for **XIII**, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl are hydrocarbons optionally interrupted by a functional group including at least one non-carbon element. In one embodiment, the functional group including at least one non-carbon element is selected from the group consisting of O, S, Se, silane, silyl ether, carbonyl, carboxyl, carboxylate, ether, ester, anhydride, acyl, cyano, $NO_2$, alkyloxy, aryloxy, hydroxy, hydroxyalkyl, amino, alkylamino, arylamino, amido, thioalkyl, thioaryl, sulfonate, phosphate, phosphonate, phosphane and stannane.

Thus, another aspect of the present invention provides a method for performing an asymmetric olefin metathesis reaction comprising providing a substrate comprising at least one olefin group associated with a ring structure, such as structure **XIII** above. An olefin group "associated with a ring structure" refers to an olefin positioned about a ring such that a ring-opened product occurs. The method involves reacting a catalyst with the substrate to initiate an olefin metathesis reaction to achieve a $k_{rel}$ of at least about 5, preferably at least about 10 and more preferably at least about 20. In one embodiment, the reaction further comprises a kinetic resolution.

Another aspect of the present invention provides a method for performing an asymmetric olefin metathesis reaction. In one embodiment, the method comprises providing two substrates, each substrate containing at least one diene group. A catalyst initiates a reaction with the substrates to form a product having an enantiomeric excess of at least about 50%.

In one embodiment, one of the substrates comprises an olefin associated with a ring structure, such as structure **XIII**. FIGs. 7-9 show such example reactions. The products of FIGs. 7-9 comprise ring-opened structures which can result from a ring-opening metathesis reaction, a cross-metathesis reaction or a combination thereof.

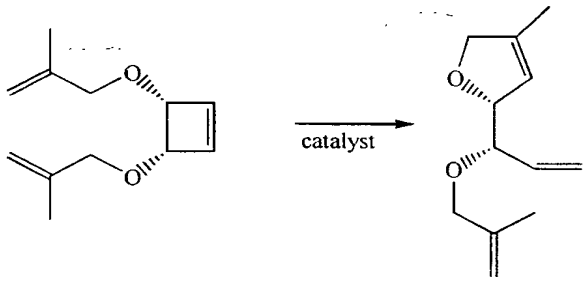
In another embodiment, the molecular substrate comprises a structure:



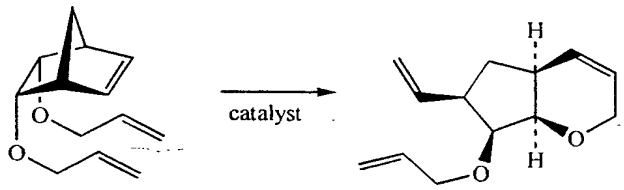
**XIV**

**XIV** is related to **XIII** in that " ┃ " represents a double bond and accordingly, both a and b equal 1. $R^1$ - $R^3$, X, Y, Z, m, n, o, p, q and r are as defined for **XIII**. In **XIV**, $R^4$ and $R^5$ can be the same or different and each of $R^4$ and $R^5$ is selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl are hydrocarbons optionally interrupted by a functional group including at least one non-carbon element.

Non-limiting examples of ring-opening metathesis reactions are illustrated in eqs 16 and 17:

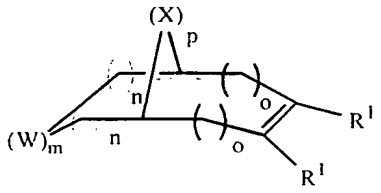



(16)



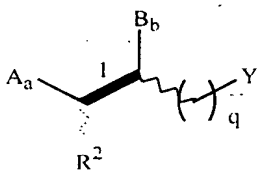

(17)

In another embodiment, the molecular substrate is a first molecular substrate and the method further comprises the addition of a second molecular substrate. The metathesis reaction can be a cross-metathesis reaction, allowing the formation of both cyclic and acyclic products. In this embodiment, the first molecular substrate can be selected from the group consisting of:



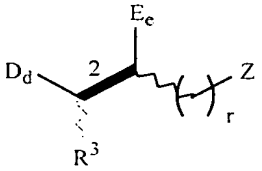

XV

and




XVI

and the second molecular substrate comprises a structure:

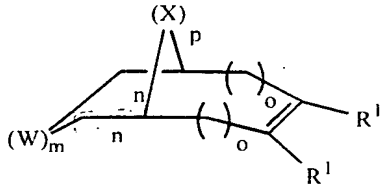



XVII

In **XVI** and **XVII**, "1┃" and "2┃" can be the same or different and each of "1┃" and "2┃" denotes a bond selected from the group consisting of a double bond and a triple bond. In **XV**, W and X can be the same or different and W and X can be any functional substituent. In another embodiment, each of W and X can be selected from the group consisting of $CR^8R^9$, carbonyl, ester, $SiR^8R^9$, $OSi(R^8)(R^9)$, $SnR^8R^9$, O, S, Se, $NR^8$, $PR^8$, $PO_3R^8$. $R^8$ and $R^9$ can be the same or different and each of $R^8$ and $R^9$ is selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. a, b, d and e can be the same or different and each of a, b, d and e are integers equaling 0 to 1. m, n, o, p, q and r can be the same or different and each of m, n, o, p, q and r are integers preferably equaling 0-20, and more preferably equaling 0-10. A, B, D, E and $R^1$ - $R^3$ can be the same or different and each of A, B, D, E and $R^1$ - $R^3$ can be selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. In **XVI** and **XVII**, Y and Z can be the same or different and each of Y and Z is selected from the group consisting of CN, carboxylic ester, amide, acid, halogen, hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl. In all embodiments for **XV** - **XVII**, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl are hydrocarbons optionally interrupted a functional group including at least one non-carbon element. In one embodiment, the functional group including at least one non-carbon element selected from the group consisting of O, S, Se, silane, silyl ether, carbonyl, carboxyl, carboxylate, ether, ester, anhydride, acyl, cyano, $NO_2$, alkyloxy, aryloxy, hydroxy, hydroxyalkyl, amino, alkylamino, arylamino, amido, thioalkyl, thioaryl, sulfonate, phosphate, phosphonate, phosphane and stannane.

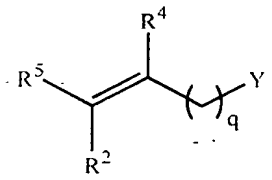
In another embodiment, the first molecular substrate can be selected from the group

consisting of:



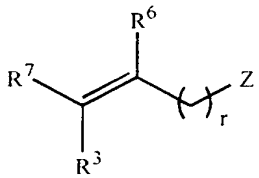
XV

and



XVIII

Where the first molecular substrate comprise structure **XV**, a ring-opening metathesis reaction can occur. The second molecular substrate comprises a structure:



XIX

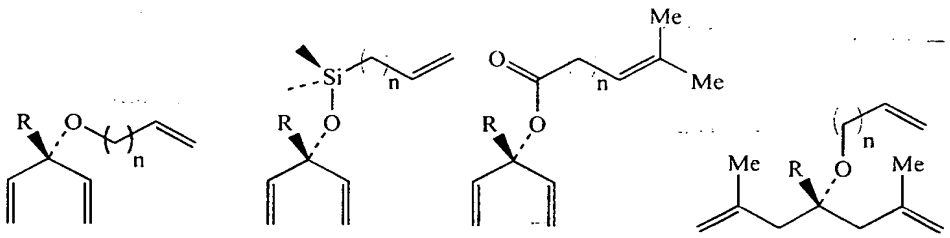
**XVIII** is related to **XVI** and **XIX** is related to **XVII** in that both "1" and "2" represent double bonds. $R^1$ - $R^3$, W, X, Y, Z, m, n, o, p, q and r are as defined previously for **XV** - **XVII**. In **XVIII** and **XIX**, $R^4$ - $R^7$ can be the same or different and each of $R^4$ - $R^7$ is selected from the group consisting of hydrogen, $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl, wherein $C_1$-$C_{20}$ alkyl, $C_1$-$C_{20}$ alkenyl, $C_1$-$C_{20}$ aryl and $C_1$-$C_{20}$ alkynyl are hydrocarbons optionally interrupted by a functional group including at least one non-carbon element.

Another aspect of the invention provides a method for catalytic desymmetrization in the absence of a solvent. A catalyst and a molecular substrate are provided, the substrate having a plane of symmetry. A desymmetrization reaction is allowed to occur in the absence of solvent to form a product free of a plane of symmetry. Performing catalytic reactions in the absence of solvent is an industrially advantageous feature. Elimination of highly volatile solvents can reduce the toxicity level. In addition, the expense of running the reaction is reduced. In one embodiment, the desymmetrization reaction can be a carbon-carbon bond formation reaction such as an olefin metathesis reaction and any previously discussed substrate can be used under solvent-free conditions.

Another aspect of the present invention provides a method for catalytic desymmetrization to form a quaternary carbon center. A quaternary carbon center is defined as a carbon atom bound to four non-hydrogen elements. In another embodiment, the four non-hydrogen elements can be carbon. In a preferred embodiment, the quaternary carbon

center is a chiral center. In general, quaternary carbon centers are difficult to form using conventional asymmetric synthesis techniques. Thus a feature of this aspect of the invention is the use of olefin metathesis to provide a general route to asymmetric quaternary carbon centers. A catalyst and a molecular substrate are provided, the molecular substrate having a plane of symmetry. A desymmetrization reaction is allowed to occur to form a product having a quaternary carbon center at a turnover number of at least about 5 in at least about 20% enantiomeric excess, preferably at least about a 50% enantiomeric excess, more preferably at least about an 85% enantiomeric excess, more preferably still at least about a 90% enantiomeric excess, more preferably still at least about a 95% enantiomeric excess and more preferably still at least about a 99% enantiomeric excess.

In one embodiment, the molecular substrate can comprise a structure selected from the group consisting of **VI - XIX**. Each of these structures can provide a quaternary carbon center when $R^1$ is a non-hydrogen element and the ring-closing olefin metathesis reaction does not solely involve two symmetric alkene or alkyne groups. Due to the plane of symmetry present in the substrate, the substrate is not optically active. Enantioselectivity is achieved upon ring formation. Examples of substrates in accordance with this aspect of the invention include:




R is a non-hydrogen element. In addition, eqs 7 and 8 illustrate the formation of asymmetric quaternary carbon centers.

The function and advantage of these and other embodiments of the present invention will be more fully understood from the examples below. The following examples are intended to illustrate the benefits of the present invention, but do not exemplify the full scope of the invention.

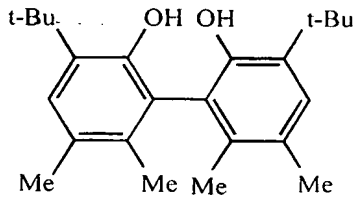
General Experimental Conditions

All reactions were conducted in oven (135°C) and flame-dried glassware under an

inert atmosphere of dry argon. Benzene and toluene were distilled from sodium metal/benzophenone ketyl, dichloromethane was distilled from calcium hydride. $Mo(NAr)(CHCMe_2Ph)(OTf)_2 \cdot DME$ was synthesized according to the procedure outlined by Schrock et al. in *J. Am. Chem. Soc.*, **1990**, *112*, 3875-3886.

Example 1: Preparation and Resolution of t-$Bu_2Me_4BiphenH_2$

The compound t-$Bu_2Me_4BiphenH_2$ was prepared from commercially available 3,4-




dimethylphenol. Potassium dichromate (54 g, 0.184 mol) in sulfuric acid (100 mL) and water (300 mL) was slowly added over 10 minutes to an acetic acid (550 mL) solution of 3,4-dimethyl-2-*tert*-butylphenol (137 g, 0.544 mol) at 60 °C. The color went from orange to green and a tan precipitate formed. The reaction was then heated for one hour at 60 °C and then cooled to room temperature. The reaction was filtered, and the brown solid was washed with water (2 x 250 mL) and methanol (3 x 200 mL). The remaining off-white solid was dried *in vacuo* to give (±)-$BiphenH_2$ (54.4 g, 50%).

Example 2: Resolution of (S) $BiphenH_2$ via $BiphenPO_2H$

Potassium hydride (12.42 g, 0.310 mol) was added in portions over an hour to a THF solution (550 mL) of (±)-$BiphenH_2$ (54.4 g, 0.154 mol). Hydrogen gas evolved, and the solution turned brown. After two hours of stirring, phosphorusoxychloride (25.9 g, 0.169 mol) was slowly added, and the solution became opaque, bleaching to a pale yellow. After stirring at room temperature for one hour, the reaction was filtered through Celite to remove potassium chloride. Water (27 mL, 10 eq) and triethylamine (85 mL, 4 eq) were added and the mixture was heated to reflux for five hours in order to hydrolyze the P-Cl bond. After cooling to room temperature, the volatiles were removed on a rotary evaporator. The triethylamine salt was slurried in hydrochloric acid (6 N, 1 L) and heated to 110 °C for five hours, and the solid became bone white. The slurry was then filtered and washed with water (2 x 250 mL), and dried *in vacuo* (61.9 g, 97% from (±)-$BiphenH_2$). The crude acid was

recrystallized twice from refluxing glacial acetic acid and dried under a stream of air. To remove residual acetic acid, the purified (±)-BiphenPO$_2$H was taken up in $CH_2Cl_2$, washed with water (3 x 250 mL), dried over $MgSO_4$, and evaporated to dryness affording pure (±)-BiphenPO$_2$H (35 g, 55%).

The biphenyl phosphoric acid, (±)-BiphenPO$_2$H, (23.8 g, 57.2 mmol) and (-)-cinchonidine (16.8 g, 57.2 mmol) were dissolved in refluxing absolute ethanol (600 mL) and allowed to stand at room temperature for an hour. The ethanol was removed with a rotary evaporator, and the residue was redissolved in ethyl acetate (250 mL). The solution was concentrated to 200 mL, and acetone (50 mL) was added. Microcrystals of the racemic salt precipitated (25.9 g, 64%, $^{31}$P NMR (EtOH) d -0.257 and -0.366). A second crop was collected which was optically pure ($^{31}$P NMR (EtOH) d -0.257). The racemate was dissolved in 1:1 methanol:ethyl acetate (100 mL total). The solution was concentrated to 70 mL to remove some of the methanol and acetone (~ 50 mL) was then added. Optically pure microcrystals were collected (9.23 g): $^{31}$P NMR (EtOH) d -0.257 ppm.

The optically pure salt (9.23 g) was dissolved in refluxing ethanol (100 mL) and hydrochloric acid was added (6 N, 100 mL). A white powder immediately precipitated, but the reaction was maintained at 70 °C for one hour before filtering. The solid was washed with water and dried *in vacuo* for several hours to give pure (S)-BiphenPO$_2$H (4.88 g, 90%).

The resolved acid (4.88 g, 11.7 mmol) was dissolved in *N,N*-dimethylacetamide (54 mL) and dimethyl sulfate (2.95 g, 23.4 mmol) was then added under an argon purge. After stirring for ten minutes, sodium bicarbonate (2.16 g, 25.8 mmol) was added as a solid to the reaction mixture and a gas evolved. The reaction was allowed to stir overnight. The solvent was then removed by vacuum distillation (60-70 °C, 500 mTorr), leaving a pale pink residue. The solid was dissolved in $CH_2Cl_2$ (100 mL) and washed with water (2 x 100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated to give the methyl ester, (S)-BiphenPO$_2$Me (4.48 g, 89%).

The methyl ester (4.48 g, 10.4 mmol) was taken up in toluene (75 mL), and Red-Al® (65% wt in toluene, 7.4 mL, 24.4 mmol) was added slowly to the reaction mixture over 25 minutes by syringe. The solution turned yellow on full addition of the Red-Al® and a gas evolved. The mixture was stirred for ten hours and then ethyl acetate (100 mL) and hydrochloric acid (1 N, 100 mL) were added. The layers were separated and the organic phase was washed with aqueous sodium bicarbonate and water. The organic layer was dried

over $MgSO_4$, the drying agent was then removed by filtration, and the solvent evaporated to give pure (S)-BiphenH$_2$ (3.1 g, 80%). Note that volatile phosphines were formed as byproducts in this reaction and all glassware should be washed with bleach after use. The optical rotation was determined to be ($[a]_D$ = -53.0 (THF, c = 0.352)).

Example 3: Resolution of (R) and (S) BiphenH$_2$ via BiphenP(O)Men*

A solution of (1R, 2S, 5R)-(-)-menthol (44 g, 282 mmol) in $CH_2Cl_2$ (100 mL) was added to a 0 °C solution of phosphorus trichloride (1.5 eq, 58 g, 423 mmol) in $CH_2Cl_2$ (200 mL) over 30 minutes. The ice bath was removed. After one hour at room temperature, the volatiles were removed *in vacuo*. The oil was redissolved in $CH_2Cl_2$ (250 mL) and a $CH_2Cl_2$ (400 mL) solution of triethylamine (3 eq, 118 mL, 847 mmol) and (±)-BiphenH$_2$ (100 g, 282 mmol) was added over 30 minutes. After two hours the reaction mixture was filtered and hydrogen peroxide (30%, 200 mL) was added slowly with stirring (CAUTION: extremely vigorous reaction). The biphasic mixture was stirred rapidly for two hours and then the layers were separated. The organic phase was washed with water and brine (200 mL) and dried over $MgSO_4$. The drying agent was removed by filtration and the solution was concentrated by rotary evaporation to a white solid. The solid was dried *in vacuo* to afford (±)-BiphenP(O)Men* (124 g, 85%): $^{31}$P NMR d -3.37 ((S)-BiphenP(O)Men*), d -4.89 ((R)-BiphenP(O)Men*).

The diastereomeric mixture of phosphates was dissolved in a minimum amount of refluxing acetic acid (~450 mL). After the solution was left at room temperature for 16 hours, white crystals formed. These were collected by filtration and washed with cold acetic acid (2 x 50 mL). The solid was then dried *in vacuo* to give (S)-BiphenP(O)Men* (42 g, 97-99% de). This material was recrystallized from refluxing acetic acid to afford (S)-BiphenP(O)Men* (37.8 g, >99% de, corresponding to 61% of (S) diastereomer).

The liquor from the first crystallization was concentrated *in vacuo* to give a solid enriched with (R)-BiphenP(O)Men*. This solid was recrystallized from refluxing MeOH (300 mL). On cooling to 0 °C, white crystals formed (32 g, ~98% de). This solid was recrystallized a second time from refluxing MeOH to give (R)-BiphenP(O)Men* in two crops (26.8 g, >99% de, 43% (R) diastereomer).

The MeOH solution was concentrated to give approximately (±)-BiphenP(O)Men* which was reused in subsequent resolution processes. Consequently the effective yield of

both (R) and (S)-BiphenP(O)Men* is higher than the 43% and 61% respective yields reported above.

Resolved (S)-BiphenP(O)Men* (37.83 g, 70.3 mmol) was dissolved in toluene (500 mL) in a 2 L round bottom Schlenk flask equipped with an addition funnel. Red-Al® (53 mL, 65% wt in toluene) was introduced into the addition funnel by cannula and then added dropwise at 0 °C onto the phosphate solution with effervescence. The reaction was stirred at room temperature for 16 hours and then carefully quenched with water (75 mL) and bleach (75 mL). The slurry was filtered through Celite, the pad was washed with toluene (250 mL), and the layers separated. The toluene layer was washed with bleach and brine (200 mL each) and then dried over $MgSO_4$. The drying agent was removed by filtration and the toluene was removed by vacuum distillation at 0 °C to give a white solid. The menthol was removed by repeated trituration with MeOH (50 mL/wash) until the minty odor disappeared. The resolved (S)-BiphenH$_2$ was collected by filtration and dried *in vacuo* (17.5 g, 70%, >99% ee). The optical purity of (S)-BiphenH$_2$ was tested by $^{31}$P NMR of the (S)-BiphenPMen* derivative. The reduction of (R)-BiphenP(O)Men* to (R)-BiphenH$_2$ followed an identical procedure.

Example 4: Mo(N-2,6-i-$Pr_2C_6H_3$)(CHCMe$_2$Ph)[(-)-t-Bu$_2$Me$_4$Biphen] (**1a**)

Potassium hydride (3 eq, 1.2 g, 30 mmol) was added in portions to a THF (100 mL) solution of (S)-BiphenH$_2$ (3.54 g, 10 mmol). After stirring for 18 hours at room temperature, solid Mo(N-2,6-$^i$Pr$_2$Ph)(CHCMe$_2$Ph)(OTf)$_2$•DME, (0.99 eq, 7.83 g, 9.9 mmol) was added to the reaction mixture and the solution became ruby red. The solution was stirred for 3 hours and then concentrated *in vacuo*. The red solid was extracted with benzene (30 mL), the suspension was filtered through Celite, and the pad was washed with benzene until colorless. The benzene was removed *in vacuo*, and the residue dissolved in ether (30 mL). The volume was reduced to ~10 mL and allowed to stand at 20 °C for 2 hours. (S)($^i$Pr$_2$)Mo(Neo) was collected as red microcrystals in four crops and dried *in vacuo* (5.81 g, 78%):

Example 5: Mo(N-2,6-Me$_2$C$_6$H$_3$)(CHCMe$_2$Ph)[(-)-t-Bu$_2$Me$_4$Biphen] (**1b**)

This complex was prepared in the same method as for Mo(N-2,6-i-$Pr_2C_6H_3$)(CHCMe$_2$Ph)-[(-)-t-Bu$_2$Me$_4$Biphen] with one exception. Dissolving the pentane extract in benzene and then removing the solvent under vacuum gave a red sponge which

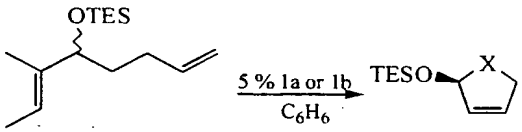
became a powder after crushing.

Example 6: Kinetic Resolution of Acyclic Dienes

**Representative procedure for Mo-catalyzed kinetic resolution.** Referring to FIG. 10 and Table 4, unsaturated silyl ether **24a** (58 mg, 0.228 mmol) was dissolved in anhydrous benzene (2.3 mL). The vessel was then charged with the optically active catalyst (-)-1 (8.6 mg, 0.011 mmol, 5 mol %) and the flask sealed with a teflon cap. After 30 min, the reaction was opened to air and MeOH was added (1 mL). The volatiles were removed on a rotary-evaporator providing a dark brown residue which was passed through a plug of silica gel using 10.1 Hexane:$Et_2O$ as the solvent. Organic solvents were then removed to yield a yellow oil (55.1 mg, 95% mass balance: assuming 78% conversion and all biphen$H_2$). The percent conversion was determined by analysis of the $^1H$ NMR spectrum (400 Mhz, $CDCl_3$; recovered 4a shows signal at δ 5.82 ppm (1H), **25a** shows a signal at δ 5.47 (1H) and δ 4.63 (1H), and the dimer shows a signal at δ 5.35 (4H) and δ 3.94 (2H). The starting material **24a** and ring-closed product **25a** can be purified by silica gel chromatography (distilled hexanes as the solvent) to afford pure **(R)-24a**. The stereochemical identity of the recovered starting material was determined by comparison with authentic non-racemic material obtained from RCM of the non-racemic allylic ethers. Non-racemic parent allylic alcohols were prepared by the method of Sharpless: Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masumune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* 1987, 109, 5675-5780.

Example 7: Conditions for the Kinetic Resolution of 4-triethylsilyloxide-5-methyl-1,6-octadiene

Both **1a** and **1b** efficiently ring-close the substrate, 3-methyl-4-triethylsiloxide-2.7-diene, over several hours (eq 18). As an example, the optically active catalyst **1a** (73 mg,




(18)

0.0984 mmol, 5%) was dissolved in toluene or benzene (20 mL). The substrate was then added and the flask sealed with a plastic cap. After a period of time (1.5 or 23 hours), the reaction was opened to air and methanol added (1 mL). The volatile compounds were

removed on a rotary evaporator and the resulting liquid was passed through an alumina plug with ether. The ether was removed affording a yellow liquid (470 mg, 95% mass conservation: assuming 50% conversion and all biphen$H_2$). The percent conversion was determined by integration of $^1H$ NMR (500 MHz, $CDCl_3$) signals: starting material (3.9 ppm) and ring-closed product (average of 4.6 and 5.45 ppm). Full NMR data for this substrate has been reported in the literature. The ring-closed product is separated from the substrate and Biphen$H_2$ by column chromatography on silica with 100% hexane gradually shifting to 10% $CH_2Cl_2$ in hexane. The diene and Biphen$H_2$ (198 mg) and ring-closed product (170 mg) were collected separately. On standing overnight, Biphen$H_2$ crystallized from resolved the substrate and was recycled. The triethylsilyl group is removed by treatment with fluoride ion in wet tetrahydrofuran.

Example 8: Procedure for desymmetrization of trienes (**6**) and (**8**)

Structures of substrates and products can be found in Table 5. A 10 mL round bottom flask was charged with 3-allyl-(2,4-dimethyl-1,4-pentadienyl)ether (**6**) (1.22 g, 8.00 mmol) in a glove box under an atmosphere of argon. The solution was subsequently charged with 1 mol % of **1b** (54.0 mg, 0.80 mmol). The solution became dark red as the catalyst dissolved with vigorous gas evolution. The flask was capped with a septum with an 18 gauge needle inserted to vent the reaction to the glove box atmosphere. After 13 h, the reaction vessel was removed from the glove box, the mixture was exposed to air and a short path distillation head was attached to the flask. The product was collected in 98.5 % purity as a colorless liquid (850 mg, 86.0 %) by distillation under nitrogen at 128°C. Trace impurities were removed by silica gel chromatography (99:1 pentanes:ether), however the isolated yield is reduced to 60-65% due to product volatility. Results are summarized in Table 5.

Example 9: Determination of stereochemical identity of catalytic desymmetrization products

As illustrated in the scheme of Fig. 11, alcohol **88**, obtained from the alkylation of isobutyraldehyde with 2-propenylmagnesiumbromide, was resolved by asymmetric epoxidation conditions of Sharpless to provide optically enriched alcohol (R)-**88**. Subsequent allylation, followed by catalytic RCM (5 mol%, (rac) **1b**) resulted in the formation of optically enhanced dihydrofuran (R)-**90**. The stereochemical configuration was equivalent to that of the catalytic hydrogenation of (**87**).

Example 10: Representative procedure for Mo-catalyzed desymmetrization of quaternary center-containing trienes

Referring to Table 5, triene **10** (32.4 mg, 0.123 mmol) was dissolved in anhydrous benzene (1.23 mL). The vessel was then charged with the optically active catalyst (-)-**1a** (4.29 mg, 0.00613 mmol, 5 mol%) and sealed with a teflon cap. After 24 h, the reaction was opened to air and MeOH was added (0.250 mL). The volatiles were removed on a rotary evaporator providing a dark brown residue. Purification by silica gel chromatography (500:1 hexane:$Et_2O$ as the solvent) afforded 8.20 mg of **11** (0.0347 mmol, 28.2% yield) and 2.30 mg of substrate dimer. The percent conversion was determined by $^1H$ NMR (400 MHz) analysis of the unpurified mixture.

Example 11: Procedural modifications for triene **12**

The procedure for triene **12** was similar to that used for triene **10** with a few modifications. Triene **12** was dissolved in benzene (0.5 M), and the mixture (after addition of the catalyst), was allowed to stir for 15 h. The enantiomeric excess was determined by chiral GLC analysis of the derived alcohol (Betadex 120 column) obtained through 9BBN hydroboration of product **13**.

Example 12: Procedural modifications for trienes **14** and **16**

The procedure used for ARCM of trienes **14** and **16** was similar to that employed for the reactions of triene **10** (see Example 11), but with a few modifications. Trienes **14** and **16** were dissolved in toluene to a concentration of 0.5 M and cooled to -20°C. The temperature was allowed to remain at -20°C for the duration of the transformation.

Example 13: (R)-(+)-Mo(N-2,6-$iPr_2C_6H_3$)(CHCMe$_2$Ph)(-3,3'-Bis (2,4,6-triisopropylphenyl)-2,2'-dihydroxy-1,1'-dinaphthyl)(THF) (**2a**)

FIG. 12 shows a schematic of the formation of the *R* isomer of binaphthol **53**. Step a of FIG. 12: TMEDA, *n*-BuLi, $Et_2O$, 22°C, 4 h; $Br_2$, $Et_2O$, -40°C → 22°C, 8 h (71% overall); Step b: 1.0 mol% $(PPh_3)_2NiCl_2$, 2,4,6-tri(isopropyl)phenyl magnesium bromide, $Et_2O$, 45°C, 24 h, 70%; Step c: $BBr_3$, $CH_2Cl_2$, 22°C, 12 h, 83%; Step d: benzylpotassium, THF, 10 min; Mo(CHCMe$_2$Ph)(NAr)$(OTf)_2$•dme, THF, 22°C, 15 min, 64% (Ar = 2,6-diisopropylPh).

**(*R*)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-dinaphthyl (52)**. A solution of n-BuLi (28

mL, 2.5 M in hexanes, 70, mmol) and tetramethylethylenediamine (TMEDA; 7.80 g, 67.0 mmol) is added to $Et_2O$ (500 mL) and allowed to stir for 15 min. To this solution is added solid (*R*)-2,2'-dimethoxy-1,1'-dinaphthyl-(10.0 g, 31.8 mmol). After 4 h, the brown dilithium salt precipitates from solution. The reaction mixture is then cooled to -35°C, and $Br_2$ (8.0 ml, 65.3 mmol) is added over a period of 0.5 h. The resulting white suspension is allowed to warm to 22°C and stirred for 2 h. At this point, the mixture is cooled to 0°C and 50 mL water is added. Aqueous extraction with $Et_2O$ (3 x 50 mL), is followed by drying of the organic layers over anhydrous $MgSO_4$ and removal of the volatiles in vacuo. At this point, (*R*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-dinaphthyl **(52)** precipitates from the ether solution as a white solid (9.90 g, 66% yield). The $^1H$ NMR spectrum proved to be identical to that reported in the literature. Lingenfelter, D.S.; Helgeson, R.C.; Cram, D.J. *J. Org. Chem.* **1981,** *46*, 393-406. $[\alpha]_{589}$=+71.4, (c=1.4, THF).

**(2,4,6-Triisopropylphenyl)magnesium bromide.** A three neck round-bottom flask containing Mg (3.00g, 125 mmol) was equipped with a condenser and an addition funnel. 10.0 mL of a 1.4 M solution of 2,4,6-triisopropylphenyl bromide (20.0 g in 50 mL $Et_2O$, 70.6 mmol) was added to the flask through the addition funnel. After 5 min, 0.20 mL (0.002 mmol) of 1,2-dibromoethane was added to the mixture. Once the solution begins to reflux, the remaining 2,4,6-triisopropylphenyl bromide solution is slowly added over 1 h. After the addition is complete, the reaction is allowed to reflux for 12 h. The resulting Grignard reagent is then titrated and stored in a dry box.

**Rac- and (*R*)-3,-'-Bis(2,4,6-triisopropylphenyl) -2,2'-dimethoxy-1,1'-dinaphthyl.** (*R*)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-dinaphthyl (4.0 g, 8.5 mmol) and $Ni(PPh_3)_2Cl_2$ (0.60g, 11 mol %, 0.90 mmol) are suspended in 100 mL $Et_2O$. To this suspension is added (2,4,6-triisopropylphenyl)magnesium bromide (0.8 M, 31.7 mL, 25.4 mmol) slowly at 22°C. The mixture was allowed to stir at 22°C for 10 min; at this point, the resulting dark green solution is refluxed for 24 h. The reaction is then allowed to chill to 0°C and quenched slowly by the addition of 50 mL of a 1.0 M solution of Hcl. The resulting aqueous layer is separated from the $Et_2O$ layer, and washed three times with excess $Et_2O$ (50 mL). The resulting organic layers where then dried over $MgSO_4$; volatile solvents are removed in vacuo to afford the unpurified residue as a white solid which is then recrystallized from $CH_2Cl_2$/hexanes to afford (*R*)-3,3'~bis(2,4,6-triisopropylphenyl)-2,2'-dimethoxy-1,1'-dinaphthyl as a white solid (4.7g, 77% yield).

**Rac- and (*R*)-3,-'-Bis(2,4,6-triisopropylphenyl) -2,2'-dimethoxy-1,1'-dinaphthyl (53).** A solution of 3,3'-Bis(2,4,6-triisopropylphenyl)-2,2'-dimethoxy-1,1'-dinaphthyl (4.0g, 5.60 mmol) in 150 mL $CH_2Cl_2$ is charged with 39.0 mL of a 1.0 M $Bbr_3$ solution in $CH_2Cl_2$ (38.9 mmol) slowly at 0°C. The resulting mixture is allowed to warm to 22°C and stirred for 12 h. The mixture is then cooled to 0°C, and reaction is quenched by the slow addition of 50 mL water. Aqueous extraction with $CH_2Cl_2$ (3 x 50 mL), followed by drying of the organic layers over $MgSO_4$ and removal of the solvents *in vacuo* to afford an off-white solid, which is washed with hexanes, filtered, and dried in vacuo to afford 3.76 g of white powder (5.44 mmol, 97% yield). Crystals of (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-2,2'-dihydroxy-1,1'-dinaphthyl **(53)** were obtained through slow evaporation of solvent from a $CH_2Cl_2$ solution.

To a stirred solution of (R)-3,3'-Bis(2,4,6-triisopropylphenyl)-2,2'-dihydroxy-1,1'-dinaphthyl (3.4 g in 250 mL THF, 4.9 mmol) is added benzyl potassium (1.34g, 10.3 mmol) slowly at 22 °C. The resulting solution turns from colorless to yellow over the course of 10 min. At this point, Mo(n-2,6-$iPr_2C_6H_3$)(CHCMe$_2$Ph)(OTf)$_2$ •(DME) (3.5 g, 4.4 mmol) is added in a single portion. After mixture is allowed to stir at 22°C for 15 min, volatile solvents are removed in vacuo from the resulting red solution to yield a dark red solid. This residue is washed with 20 mL of benzene and filtered through celite. Removal of solvents in vacuo affords a red solid, which was washed with cold $Et_2O$ (5 mL) and again filtered through celite. The $Et_2O$ solution is cooled to -35°C to afford 2.0 g (36% yield) of **2a** as a yellow solid.

Example 14: (R)-(+)-Mo(N-2,6-$iPr_2C_6H_3$)(CHCMe$_2$Ph)(-3,3'-Bis (2,4,6-triisopropylphenyl)-2,2'-dihydroxy-1,1'-dinaphthyl)(THF) (**2b**)

Complex **2b** was synthesized according to the above procedures, except that Mo(N-2,6-$Me_2C_6H_3$)(CHCMe$_2$Ph)(OTf)$_2$•dme was used as the starting material.

Example 15: Representative procedure for Mo-catalyzed kinetic resolution (at 22°C)

Referring to FIGs. 4 and 5 and Tables 1 and 2, 2-Methyl-3-*tert*-butyldimethylsiloxy-1,7-octadiene **(55b)** (0.15 g, 0.59 mmol) is dissolved in benzene (5.9 mL) in a loosely-capped vial (to allow for the release of ethylene). Optically pure catalyst **(2a)** 0.034 g, 0.029 mmol, 5 mol %) is then added. The resulting orange mixture is allowed to stir at 22°C for ~3.5 h. At this point, the reaction mixture is exposed to air; subsequently, methanol (1 mL) is added.

Removal of the volatiles in vacuo affords a dark red oil. Percent conversion is calculated by analysis of the $^1H$ NMR spectrum (500 MHz, $CDC1_3$). The starting material, metathesis product, and dimeric products are isolated by silica gel chromatography (hexanes). In the case of highly volatile products, percent conversion is determined by the analysis of the $^1H$ NMR spectrum of the unpurified reaction mixture ($C_6D_6$).

For temperatures above 22°C, 2-Methyl-3-*tert*-butyldimethylsiloxy-1,7-octadiene **(55b)** (0.15 g, 0.59 mmol) is dissolved in benzene (5.9 mL) in a tightly-capped vial (to prevent solvent loss). Optically pure catalyst **(2a)** (0.034 g, 0.029 mmol, 5 mol %) is added to this solution as a solid. The resulting orange solution is placed into a heated bath (equilibrated to 60°C) for ~35 min. At this time, the reaction mixture is exposed to air and methanol (1 mL) is added. In analogy to the purification procedure mentioned above, the percent conversion was determined, and starting material, metathesis product, and dimeric product were isolated. In the case of highly volatile products, percent conversion was determined by analysis of the $^1H$ NMR of the unpurified reaction mixture ($C_6D_6$).

**Determination of the stereochemical identity of Mo-catalyzed kinetic resolution products**. A sample of optically enriched (*R*)-**57** was prepared through silyation of a sample of optically enriched allylic alcohol, prepared by the method of Sharpless. Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5767-5780 and references cited therein. The product obtained from the Mo-catalyzed ARCM was correlated with this authentic material.

Example 16: Catalytic Asymmetric Desymmetrization of Trienes

FIG. 6 shows example triene substrates and Table 3 shows the results of the desymmetrization. The procedures of Example 15 were followed.

Example 17: Determination of the stereochemical identity of catalytic desymmetrization products

As illustrated in FIG. 13, Ti-catalyzed kinetic resolution of allylic alcohol **77**, followed by the installment of the requisite allylsilyl chloride led to the formation of optically-enriched (*R*)-**78**. Subsequent catalytic RCM with 2 mol % (Mo(N-2,6-$iPr_2C_6H_3$) $CHCMe_2Ph)(OCCH_3)_2)_2$) resulted in the formation of an authentic sample of (*R*)-**76**. This material was compared by chiral GLC (BETADEX chiral column) with a sample of optically

pure (*R*)-**76**, obtained from the site-selective Rh-catalyzed hydrogenation of (*R*)-**68** (derived from Mo-catalyzed desymmetrization of **67**).

Example 18: Desymmetrization of Tetraenes by Mo-Catalyzed Asymmetric RCM

Catalysts for desymmetrization of tetraenes are shown in FIG. 14 and results are tabulated in Table 6.

Example 19: Desymmetrization of Trienes by Tandem Asymmetric Mo-Catalyzed Ring-Opening/Ring-Closing Metathesis

Catalysts for desymmetrization of trienes are shown in FIG. 15 and results are tabulated in Table 7.

Example 20: Enantioselective Desymmetrization of Dienes by Tandem Mo-Catalyzed Ring-Opening/Ring-Closing Metathesis

Catalysts for desymmetrization of dienes are shown in FIG. 16 and results are tabulated in Table 8.

Example 21: (±)-3,3'-Di-(1-adamantyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2 ,2'-diol ((±)-BiadH$_2$)

A solution of potassium dichromate (3.95 g, 13.4 mmol) in sulfuric acid (6.5 mL) and water (20 mL) was added dropwise over 20 minutes to an acetic acid (40 mL) slurry of 2-adamantyl-3,4-dimethylphenol (10.3 g, 40.2 mmol) at 65 °C. After stirring the reaction mixture for one hour at 65 °C, the green suspension was cooled to room temperature and filtered. The brown precipitate was washed with water (120 mL), triturated with methanol (3 x 75 mL), and the resulting white solid was dried *in vacuo* to afford (±)-BiadH$_2$ (5.6 g, 55% yield).

Addition of benzyl potassium (13 mg, 0.1 mmol) to a THF-$d_8$ slurry of (±)-BiadH$_2$ resulted in a clear golden solution of (±)-BiadK$_2$.

To a slurry of (±)-BiadH$_2$ (25 mg, 0.049 mmol) in THF (1 mL) was added potassium hydride (5 mg, 0.12 mmol) affording a blue solution. Men*PCl$_2$ (13 mg, 0.051 mmol) in THF (0.5 mL) was added, and the reaction became yellow with a white precipitate formed.

**Resolution of BiadH$_2$ by (±)BiadP(O)Men***

(±)-BiadH$_2$ (29.9 g, 58.6 mmol) was dissolved in THF (500 mL) and solid potassium hydride (2.1 eq, 4.9 g, 123 mmol) was added in portions. The reaction mixture became dark green and evolved hydrogen gas. After one hour, Men*PCl$_2$ was added, the solution became brown and a white precipitate formed. Water was then added slowly to quench the excess potassium hydride. The volatiles were removed by rotary evaporation, and the brown residue was taken up in $CH_2Cl_2$ (400 mL). Hydrogen peroxide (30%, 50 mL) was added and the biphasic mixture was stirred vigorously for one hour. The layers were separated and the organic phase was washed with water (200 mL) and brine (200 mL) and then dried over $MgSO_4$. The drying agent was removed by filtration and the solution concentrated to an orange foam. The diastereomeric mixture of phosphates was purified by crystallization from refluxing heptane (3 crops, 25 g total, 60%): $^{31}$P NMR ($C_6H_6$) d -3.29 and -5.57.

A Soxhlet extraction apparatus was charged with the mixture of (±)-BiadP(O)Men* diastereomers (6 g). The pot was charged with acetone (75 mL) and heated to reflux until all of the material in the filter cup dissolved (3 days). Concurrently, a precipitate formed in the pot. After cooling the reaction mixture to room temperature, the precipitate was collected by filtration (2.52 g, 99% de (S)-BiadP(O)Men*). Additional white powder was precipitated from the mother liquor and collected by filtration (1.35 g, ~0% de). The remaining acetone solution was then concentrated to give enriched (+)-BiadP(O)Men* (0.91 g, 90% de).

The diastereomerically pure phosphate, (S)-BiadP(O)Men* (7.78 g, 10.96 mmol) was dissolved in toluene (125 mL). Red-Al® (13.3 mL, 44 mmol, 65% wt in toluene) was added by syringe. After stirring for 4 days at room temperature, water (50 mL) was added slowly to quench excess Red-Al® The slurry was stirred for 10 minutes, filtered through Celite and the pad was washed liberally with toluene and bleach. The layers were separated and the organic phase was washed with bleach and brine (100 mL each) and then dried over $Na_2SO_4$. The toluene solution was decanted from the drying agent and the volatiles were removed by vacuum distillation at room temperature. The waxy white solid was washed with hexane (3 x 50 mL) until the minty aroma of (-)-menthol disappeared. Optically pure (S)-BiadH$_2$ was dried *in vacuo* (3.11 g, 56%). Optical rotation was determined ($[a]_D$ = -32.1 (THF, c = 0.033)).

Example 22: Mo(N-2-$CF_3C_6H_4$)$_2$($CH_2$$^t$Bu)$_2$ (2g')

Neopentylmagnesium chloride (52 mL, 2.27 M in ether, 117.7 mmol) was added over

30 minutes to a cooled ether (500 mL) solution of $Mo(N\text{-}2\text{-}CF_3Ph)_2Cl_2 \circ DME$, **1g**, (33.68 g, 58.6 mmol). The reaction mixture was stirred at room temperature for 12 hours and was then filtered through Celite. The pad was washed with ether until colorless. The clear red solution was then concentrated *in vacuo* to an oil. On standing overnight at -25 °C, the oil crystallized as red blocks (29 g, 73%).

Example 23: $Mo(N\text{-}2\text{-}CF_3C_6H_4)(CH^tBu)(OTf)_2 \circ DME$ (3g')

Triflic acid (15.9 g, 105.9 mmol) was dissolved in cold DME (50 mL) and then added to a cold (-25 °C) solution of $Mo(N\text{-}2\text{-}CF_3Ph)_2(CH_2{}^tBu)_2$, **2g'**, (19.63 g, 35.3 mmol) in DME (200 mL) . The reaction was stirred at room temperature for 16 hours and then concentrated *in vacuo* to a brown solid. Toluene (50 mL) was added and the solution was concentrated again *in vacuo* to remove residual DME. The brown residue was then extracted with toluene (250 mL) and benzene (200 mL) and filtered through Celite. The solution was concentrated *in vacuo*. The resulting brown solid was triturated with ether to give a yellow powder that was collected by filtration (16.3 g, 65%): $^1H$ NMR (4:1 Mixture of rotamers).

Example 24: $Mo(N\text{-}2\text{-}CF_3C_6H_4)(CHCMe_2Ph)((\pm)\text{-}Biphen) \circ THF_{0.5}(OEt_2)_{0.5}$ ($(\pm)(CF_3)Mo(Neo) \circ THF_{0.5}(OEt_2)_{0.5}$)

Solid benzyl potassium (2.02 eq, 1.29 g, 10.32 mmol) was added in portions over 10 minutes to a stirred THF (50 mL) solution of (±)-$BiphenH_2$ (1.827 g, 5.16 mmol) at room temperature. After stirring for 15 minutes, solid $Mo(N\text{-}2\text{-}CF_3Ph)(CHCMe_2Ph)(OTf)_2 \circ DME$, **3g**, (4.00 g, 5.16 mmol) was added to the reaction and the solution became dark red. The solution was stirred for two hours and then concentrated *in vacuo* to a red-brown solid. The residue was extracted with benzene (25 mL), the suspension was filtered through Celite, and the pad was washed with toluene until it was colorless. The eluent was then concentrated *in vacuo* and the residue was dissolved in ether (10 mL). The ethereal solution was filtered through a Kimwipe and the volume halved. Addition of THF (1 eq, 371 mg, 5.16 mmol) and vigorous scoring of the vial wall with a spatula induced precipitation of a dark yellow solid that was collected by filtration, washed with ether (2 mL), and dried *in vacuo* (2.01 g, 52%).

Example 25: $Mo(N\text{-}2\text{-}CF_3Ph)(CHCMe_2Ph)((\pm)\text{-}Biphen)$ ($(\pm)(CF_3)Mo(Neo)$)

Solid benzyl potassium (2.2 eq, 58 mg, 0.44 mmol) was added in portions to a

solution of (±)-BiphenH$_2$ (71 mg, 0.2 mmol) in toluene (5 mL). After 2 hours, solid Mo(N-2-CF$_3$C$_6$H$_4$)(CHCMe$_2$Ph)(OTf)$_2$∘DME, **3g**, (155 mg, 0.2 mmol) was added to the reaction and the resulting red solution was stirred for 45 minutes. The volatiles were removed *in vacuo* and the residue extracted with pentane (15 mL). The suspension was passed through Celite, and the pentane was removed *in vacuo* affording (±)(CF$_3$)Mo(Neo) as a red powder (75 mg, 51%): $^1$H NMR Mixture of rotamers $K_{eq}$ = 0.26.

Example 26: Mo(N-2-CF$_3$Ph)(CH$^t$Bu)((±)-Biphen) ((±)(CF$_3$)Mo(Np))

Solid benzyl potassium (286 mg, 2.2 mmol) was added in portions to a toluene (20 mL) solution of (±)-BiphenH$_2$ (354 mg, 1 mmol) at room temperature. After stirring for 5 hours, the reaction was cooled to -25 °C and solid Mo(N-2-CF$_3$Ph)(CH$^t$Bu)(OTf)$_2$∘DME, **3g'**, (714 mg, 1 mmol) was added. The reaction was stirred at room temperature for 45 min and then concentrated *in vacuo*. The residue was extracted with pentane (40 mL), the suspension was filtered through Celite, and the pad was washed with pentane until the eluent was very pale red. The eluent volume was reduced to 4 mL, and the solution was cooled to -25 °C overnight. The red precipitate of (±)(CF$_3$)Mo(Np) was collected by filtration, washed with cold pentane (1 mL), and dried *in vacuo* (260 mg, 38%): $^1$H NMR (Mixture of rotamers, $K_{eq}$ = 31.4).

Example 27: Mo(N-2-CF$_3$C$_6$H$_4$)(CH-2-MeOC$_6$H$_4$)((±)-Biphen) ((±)(CF$_3$)Mo(Sty))

A toluene (2 mL) solution of 2-methoxystyrene (241 mg, 1.8 mmol) was added in one portion to a toluene (6 mL) solution of (±)(CF$_3$)Mo(Neo)∘(THF/OEt$_2$) (1.217g, 1.5 mmol), and the reaction was stirred for 10 minutes. The red solution was concentrated *in vacuo*, triturated with ether (5 mL) and collected by filtration. The red powder was washed with ether and dried *in vacuo* (800 mg, 74%).

Example 28: Mo(N-2-CF$_3$Ph)(CH$^t$Bu)((±)-Biad) ((±)'(CF$_3$)Mo(Np))

Benzyl potassium (2.2 eq, 56 mg, 0.44 mmol) was added in portions to a solution of (±)-BiadH$_2$ (102 mg, 0.2 mmol) in toluene (6 mL). The reaction was stirred at room temperature for 20 hours and solid Mo(N-2-CF$_3$Ph)(CH$^t$Bu)(OTf)$_2$∘DME, **1g'**, (142 mg, 0.2 mmol) was added. After stirring for 45 minutes, the red solution was concentrated *in vacuo*. The dark red residue was extracted with pentane (5 mL), the suspension was filtered through

Celite and the pad was washed with pentane until the eluent was colorless. The solution was then concentrated to 2 mL and red microcrystals began to form. The solution was stored at -25 °C overnight and red-orange microcrystals were collected by decanting the liquor and drying *in vacuo* (68 mg, 41%).

Example 29: Mo(N-1-Adamantyl)(CHCMe$_2$Ph)((±)-Biphen) ((±)(Ad)Mo(Neo))

Benzyl potassium (267 mg, 2.05 eq, 2.05 mmol) was added in portions to a stirred THF (10 mL) of (±)-BiphenH$_2$ (354 mg, 1 mmol). After 15 minutes, solid Mo(NAd)(CHCMe$_2$Ph)(OTf)$_2$•DME, **3h**, (765 mg, 1 mmol) was added to the reaction, and the solution became dark yellow. After stirring for one hour at room temperature, the volatiles were removed *in vacuo*. The residue was taken up in pentane, the suspension was filtered through Celite, and a pale yellow powder precipitated from the light brown eluent. The yellow powder was collected by filtration and dried *in vacuo* (435 mg): $^1$H NMR (Mixture of *anti*-(±)Ad)Mo(Neo) and an unidentified decomposition byproduct).

Example 30: Mo(N-2,6-$^i$Pr$_2$C$_6$H$_3$)(CHCMe$_2$Ph)((S)-Biad) ((S)'($^i$Pr$_2$)Mo(Neo))

Solid benzyl potassium (2.04 eq, 53 mg, 4.08 mmol) was added in portions to a solution of (S)-BiadH$_2$ (102 mg, 0.2 mmol) in THF (6 mL). After 10 minutes, Mo(N-2,6-$^i$Pr$_2$Ph)(CHCMe$_2$Ph)(OTf)$_2$•DME, (158 mg, 0.2 mmol) in THF (2 mL) was added and the reaction became dark red. After one hour, the volatiles were removed *in vacuo*. The residue was then dissolved in toluene (2 mL) and concentrated again *in vacuo* to remove residual THF. The solid was then extracted with pentane (10 mL), the suspension was filtered trough Celite and the eluent volume reduced to ~1 mL. On standing for one hour at room temperature, a golden precipitate formed which was collected by filtration and dried *in vacuo* (62 mg, 34%).

Example 31: Mo(N-2,6-Et$_2$C$_6$H$_3$)(CHCMe$_2$Ph)((S)-Biad) ((S)'(Et$_2$)Mo(Neo))

Benzyl potassium (2.08 eq, 146 mg, 1.12 mmol) was added in portions to a stirred solution of (S)-BiadH$_2$ (275 mg, 0.54 mmol) in THF (30 mL). After stirring for 30 minutes, solid Mo(N-2,6-Et$_2$C$_6$H$_3$)(CHCMe$_2$Ph)(OTf)$_2$•DME, (412 mg, 0.54 mmol) was added and the reaction became dark red. After one hour, the volatiles were removed *in vacuo* and the residue was dissolved in pentane (5 mL). The red slurry was filtered through Celite and

orange microcrystals precipitated at room temperature. Two crops were collected by filtration and dried *in vacuo* (145 mg, 30%): $^1$H NMR (Mixture of rotamers $K_{eq}$ = 100).

Example 32: Mo(N-2,6-$Me_2C_6H_3$)(CHCMe$_2$Ph)((S)-Biad) ((S)'(Me$_2$)Mo(Neo))

Benzyl potassium (2.08 eq, 146 mg, 1.04 mmol) was added in portions to a stirred solution of (S)-Biad$H_2$ (255 mg, 0.5 mmol) in THF (30 mL). After stirring for 30 minutes, solid Mo(N-2,6-$Me_2C_6H_3$)(CHCMe$_2$Ph)(OTf)$_2$•DME (368 mg, 0.5 mmol) was added and the reaction became dark red. After stirring for one hour, the volatiles were removed *in vacuo* and benzene (10 mL) was added. The slurry was filtered through Celite and the eluent was concentrated *in vacuo*. The residue was dissolved in isopropyl ether (4 mL). An orange-red precipitate formed on standing at room temperature. The orange-red powder was collected by filtration, washed with cold isopropyl ether and dried *in vacuo* (190 mg, 44%).

Example 33: Mo(N-3,5-$Me_2C_6H_3$)(CHCMe$_2$Ph)((S)-Biad) ((S)'-3,5-Me$_2$)Mo(Neo))

Benzyl potassium (2.04 eq, 53 mg, 0.41 mmol) was added to a stirred solution of (S)-Biad$H_2$ (102 mg, 0.2 mmol) in THF (10 mL). After stirring for 15 minutes, a solution of Mo(N-3,5-$Me_2C_6H_3$)(CHCMe$_2$Ph)(OTf)$_2$•DME, **3d**, (147 mg, 0.2 mmol) in THF (4 mL) was added and the reaction became dark red. After one hour, the volatiles were removed *in vacuo* and the residue was dissolved in pentane (5 mL). The slurry was filtered through Celite and the eluent was concentrated *in vacuo*. The residue was dissolved in pentane (4 mL) and the solution volume was reduced to 2 mL. A yellow precipitate formed on standing at room temperature and the powder was collected by filtration (65 mg, 38%).

Example 34: Mo(N-2-$CF_3C_6H_4$)(CH$^t$Bu)((S)-Biad) ((S)'(CF$_3$)Mo(Np))

Solid benzyl potassium (2.08 eq, 135 mg 1.04 mmol) was added in portions to a stirred solution of (S)-Biad$H_2$ (254 mg, 0.5 mmol) in toluene (40 mL). Solid Mo(N-2-$CF_3C_6H_4$)(CH$^t$Bu)(OTf)$_2$•DME, **3g'**, (356 mg, 0.5 mmol) was added and the reaction became dark red. After stirring at room temperature for 1.5 hours, the solution was concentrated *in vacuo* and the residue dissolved in pentane (75 mL). The suspension was filtered through Celite and the volume reduced to approximately 5 mL. Red-orange microcrystals formed and were collected by decanting the solution. A second crop of red-orange powder was collected by filtration and dried *in vacuo*. (180 mg, 43%).

Table 1. Catalytic Enantioselective Carbocycle Synthesis by ARCM.[a]

| entry | substrate | catalyst | temp (°C); reaction time | conv (%);[b] dimer (%) | $k_{rel}$[c,d] |
|---|---|---|---|---|---|
| 1 | (±)-**55a**, R=TES | **2a** | 22; 4 h | 66; 34 | 17 |
| 2 | (±)-**55a**, R=TES | **2a** | 65; 40 min | 77; 27 | 24 |
| 3 | (±)-**55a**, R=TES | **2b** | 22; 1 h | 68; 11 | 4.3 |
| 4 | (±)-**55a**, R=TES | **1a** | 22; 30 min | 58; 11 | 4.0 |
| 5 | (±)-**55a**, R=TES | **2a** | 22; 3 h | 68; 37 | >25 |
| 6 | (±)-**55b**, R=TBS | **2a** | 65; 35 min | 65; 23 | >25 |
| 7 | (±)-**55b**, R=TBS | **2b** | 22; 1 h | 59; 23 | 2.5 |
| 8 | (±)-**55b**, R=TBS | **1a** | 22; 20 min | 82; 7 | 3.3 |

a. Conditions: 5 mol % cat., Ar atm, $C_6H_6$. b. Conversion determined by analysis of 400 MHz $^1H$ NMR of the unpurified mixture. c. Enantioselectivity determined by GLC analysis (CHIRALDEX-GTA by Alltech) in comparison with authentic racemic material. d. Relative rate determined based on the formation and selectivity of product.

Table 2. Catalytic Enantioselective Heterocycle Synthesis by ARCM.[a]

| entry | substrate | product | catalyst | time | conv (%);[b] dimer (%) | $k_{rel}$[c,d] |
|---|---|---|---|---|---|---|
| 1 | (±)-**57** | (*R*)-**58** | **2a** | 35 min | 53; 5 | >25 |
| 2 | (±)-**57** | (*R*)-**58** | **1a** | 25 min | 58; 40 | 1.9 |
| 3 | (±)-**57** | (*R*)-**58** | **1b** | 20 min | 62; 19 | 10 |
| 4 | (±)-**59** | (*R*)-**60** | **2a** | 1 h | 60; 8 | >25 |
| 5 | (±)-**59** | (*R*)-**60** | **1a** | 1 h | 54; 47 | 1.1 |
| 6 | (±)-**59** | (*R*)-**60** | **1b** | 1 h | 58; 39 | 14 |
| 7 | (±)-**61** | (*R*)-**62** | **2a** | 5 min | 62; <2 | 1.9 |
| 8 | (±)-**61** | (*R*)-**62** | **1a** | 3 min | 54; <2 | 21 |
| 9 | (±)-**61** | (*R*)-**62** | **1b** | <1 min | 55; <2 | 1.4 |
| 10 | (±)-**63** | (*R*)-**64** | **2a** | 5 min | 63; <2 | 3.0 |
| 11 | (±)-**63** | (*R*)-**64** | **1a** | 2 min | 52; <2 | >25 |
| 12 | (±)-**63** | (*R*)-**64** | **1b** | <1 min | 70; <2 | 3.7 |

a-c. See Table 1. d. Relative rates are based on the recovered substrate.

Table 3. Enantioselective Synthesis of Six-Membered Ring Heterocycles by Mo-Catalyzed Desymmetrization.[a]

| entry | substrate | product | catalyst | time (h); temp (°C) | conv (%);[c] dimer (%) | yield (%);[d] ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **65** | **(*R*)-66** | **2a** | 18;22 | <5; -- | --; -- |
| 2 | **65** | **(*R*)-66** | **2b** | 18; 22 | 80; <2 | 77; 89 |
| 3 | **65** | **(*R*)-66** | **1b** | 6; 22 | 93; <2 | 83; 99 |
| 4 | **67** | **(*R*)-68** | **2a** | 3; 60 | >99; <2 | 98; >99 |
| 5 | **67** | **(*R*)-68** | **1a** | 24; 22 | 50; 32 | 17; 65 |
| 6 | **67** | **(*R*)-68** | **1b** | 24; 22 | 51; 28 | 20; 85 |
| 7 | **69** | **(*R*)-70** | **2a** | 3; 60 | 95; <2 | 86; >99 |
| 8 | **69** | **(*R*)-70** | **1a** | 3; 22 | 72; 6 | --; 96 |
| 9 | **69** | **(*R*)-70** | **1b** | 3; 22 | 65; 38 | --; 86 |

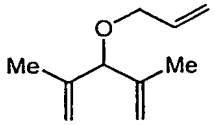
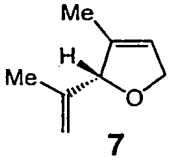
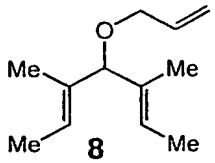
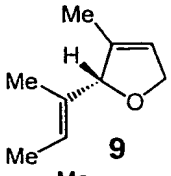
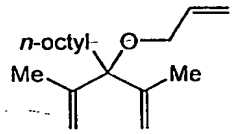
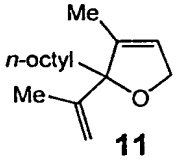
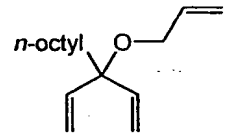
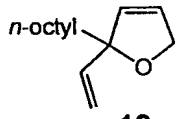
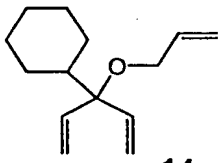
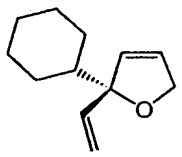
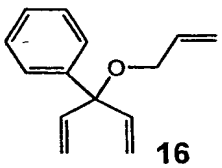
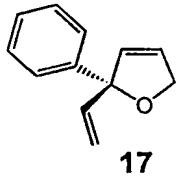
a-c. See Table 1. d. Isolated yields after silica gel chromatography. e. Reactions in entries 9 were performed in *n*-pentane due to high product volatility.

Table 4. Kinetic Resolution of Acyclic Dienes.

| entry | substrate | product | R | reaction time (min); conv (%) | percent product[b] | percent dimer[b] | unreacted substrate config. ee (%)[c] | product. ee (%)[c] | $k_{fast}/k_{slo}$ w |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 24a | 25a | a,R=TES | 10; 81 | 43 | 38 | R, >99 | 93 | 58[d] |
| 2 | 24b | 25b | b,R=TBS | 60; 75 | 42 | 33 | R, >99 | 93 | 56[d] |
| 3 | 24c | 25c | c,R=TBDPS | 120; 83 | 43 | 40 | R, 95 | 92 | 52[d] |
| 4 | 24d | 25d | d, R=Bn | 180; 76 | 41 | 35 | R, 91 | 85 | 22[d] |
| 5 | 26 | 27 | | 120; 50 | 40 | 10 | <5 | <5 | |
| 6 | 28 | 25a | | 5; 59 | 55 | <5 | R, 97 | 65 | 11[e] |
| 7 | 29 | 30 | | 120; 50 | <5 | 50 | | | |
| 8 | 31 | 32 | | 30; 58 | 47 | 11 | R, 57 | 45 | 4[e] |

[a]Reaction conditions: 5 mol % 1, $C_6H_6$, Ar atm, 22°C. Mass balance >90%. [b]Conversion determined by analysis of 400 Mhz $^1$H NMR of unpurified mixture. [c]Enantioselectivity determined by GLC analysis (CHIRALDEX-GTA by Alltech) of derived acetates in comparison with authentic material. [d]Relative rate calculated based on formation and selectivity of product (see ref. 13). [e]Relative rate determined based on the recovered starting material.

**Table 5.** Enantioselective Synthesis of Dihydrofurans by Mo-Catalyzed Desymmetrization. [a]

| entry | substrate | catalyst | temp (°C), time | product | product ee (%), config. [b] | conv., [c] yield (%) [d] |
|---|---|---|---|---|---|---|
| 1 |  **6** | **1a** | 22, 6 h |  **7** | 93, *R* | 94, 86 |
| | | **1b** | 22, 6 h | | 93, *R* | 93, 86 |
| 2 |  **8** | **1a** | 22, 9 h |  **9** | 94, *R* | 32, – |
| | | **1b** | 22, 4 h | | 99, *R* | 95, 83 |
| 3 |  **10** | **1a** | 22, 9 h |  **11** | – | NO REACTION |
| | | **1b** | 22, 4 h | | 50 | 36, 28 |
| 4 |  **12** | **1a** | 22, 15 h |  **13** | 10 | 76, 73 |
| | | **1b** | 22, 15 h | | 10 | >98, 88 |
| 5 |  **14** | **1a** | 22, 18 h |  **15** | 17, *S* | 87, 85 |
| | | **1b** | -20, 18 h | | 73, *S* | 93, 84 |
| 6 |  **16** | **1a** | 22, 18 h |  **17** | 16, *S* | 36, 34 |
| | | **1b** | -20, 18 h | | 82, *S* | 93, 91 |

a. Conditions: 5 mol % catalyst (1 mol %, entry 1), toluene for reactions at -25 °C and $C_6H_6$ for those at 22 °C, Ar atm. b. Selectivity determined by chiral GLC (CHIRALDEX-GTA by Alltech for entries 1-4; BETADEX-120 by Alltech for entries 5-6) in comparison with authentic racemic material. c. Conversion determined by GLC analysis in comparison with dodecane as the internal standard (entries 1-2) or by $^1$H NMR analysis (400 MHz). d. Isolated yields after silica gel chromatography or distillation.

Table 6. Desymmetrization of Tetraenes by Mo-Catalyzed Asymmetric Ring-Closing Metathesis.[a]

| entry | substrate | product | catalyst; mol % | time | conv (%):[b] bicycle (%)[c] | yield (%);[d] ee (%)[e] |
|---|---|---|---|---|---|---|
| 1 | 93 | 94 | 1a; 5 | 5 min | 100; >98 | --- |
| 2 | 93 | 94 | 1b; 5 | 15 min | >99; 20 | 72; >98 |
| 3 | 93 | 94 | 2a; 5 | 1 h | 30; 10 | ND; 73 |
| 4 | 95 | 96 | 1a; 5 | 14 h | 56; <2 | ND; >98 |
| 5 | 95 | 96 | 1b; 5 | 14 h | <20; <2 | ND; >98 |
| 6 | 95 | 96 | 2a; 5 | 1 h | >99; <2 | 76; >98[f] |

a. Conditions: Ar atm, 22°C. b. By GLC (Internal standard). c. By 400 MHz $^1$H NMR analysis. d. Isolated yield of purified products by silica gel chromatography (4) or distillation (6). e. By chiral GLC analysis (CD-GTA for 4, BETADEX for 6). f. Reaction carried out at 60°C. ND=not determined.

Table 7. Desymmetrization of Trienes by Tandem Asymmetric Mo-Catalyzed Ring-Opening/Ring-Closing Metathesis.[a]

| entry | substrate | product | | catalyst; mol % | time (h) | conv (%):[b] bicycle (%)[c] | yield (%);[d] ee (%)[e] |
|---|---|---|---|---|---|---|---|
| 1 | 110 | 112 | a R=H | 1a; 5 | 0.2 | >98; - | 33; 86 |
| 2 | 110 | 112 | b R=Me | 1a; 5 | 0.5 | >98; - | 69; 92 |
| 3 | 116 | 117 | a R=H | 1a; 5 | 0.2 | >98; 20 | 76; 98 |
| 4 | 116 | 117 | | 1b; 1 | 0.2 | 63; <2 | 55; 84 |
| 5 | 116 | 117 | | 2a; 5 | 48 | 30; 15 | ND |
| 6 | 116 | 117 | b R=Me | 1a; 2 | 0.2 | >98; 10 | 84; 98 |
| 7 | 116 | 117 | | 1b; 5 | 0.2 | >98; 35 | 42; 92 |

a. Conditions: Ar atm, 22°C. b. By GLC (internal standard). c. By 400 MHz $^1$H NMR analysis. d. Isolated yield of purified products by silica gel chromatography. e. By chiral GLC (CD-GTA). ND=Not determined.

Table 8. Enantioselective Desymmetrization of Dienes by Tandem Mo-Catalyzed Ring-Opening/Ring-Closing Metathesis.[a]

| entry | substrate | product | catalyst; mol % | additive (mol %) | time (h); conv (%)[b] | yield (%);[c] ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | 118 | 119 | 1a; 5 | -- | 7; 60 | ; 72 |
| 2 | 118 | 119 | 1b; 5 | -- | 24; <2 | --; -- |
| 3 | 118 | 119 | 1b; 5 | 20 (10) | 24; 85 | 54; 92 |
| 4 | 121 | oligomers | 1a; 5 | | 0.2; >98 | -- |
| 5 | 121 | oligomers | 1b; 5 | | 0.2; >98 | -- |
| 6 | 121 | oligomers | 2a; 5 | | 0.2; >98 | 10; <10 |

a-c. See Table 6. d. By chiral GLC (CD-GTA).

Those skilled in the art would readily appreciate that all parameters listed herein are meant to be exemplary and that actual parameters will depend upon the specific application for which the methods and apparatus of the present invention are used. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described.

What is claimed is: